

ARYLALKENYL AND ARYLALKYNYL SUBSTITUTED IMIDAZOQUINOLINES

RELATED APPLICATIONS

5 The present invention claims priority to U.S. Provisional Application Serial No. 60/532982, filed December 29, 2003, which is incorporated herein by reference.

FIELD OF THE INVENTION

10 This invention relates to derivatives of imidazoquinoline compounds and to pharmaceutical compositions containing the compounds. A further aspect of this invention relates to the use of these compounds as immunomodulators, for inducing cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases.

BACKGROUND OF THE INVENTION

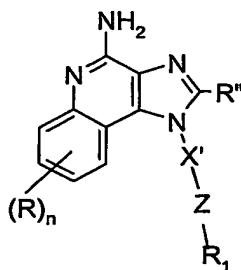
15 In the 1950's the 1*H*-imidazo[4,5-*c*]quinoline ring system was developed, and 1-(6-methoxy-8-quinoliny)-2-methyl-1*H*-imidazo[4,5-*c*]quinoline was synthesized for possible use as an antimalarial agent. Subsequently, syntheses of various substituted 1*H*-imidazo[4,5-*c*] quinolines were reported. For example, 1-[2-(4-piperidyl)ethyl]-1*H*-
20 imidazo[4,5-*c*]quinoline was synthesized as a possible anticonvulsant and cardiovascular agent. Also, several 2-oxoimidazo[4,5-*c*]quinolines have been reported.

 Certain 1*H*-imidazo[4,5-*c*]quinolin-4-amines and 1- and 2-substituted derivatives thereof were later found to be useful as antiviral agents, bronchodilators and immunomodulators. Subsequently, certain substituted 1*H*-imidazo[4,5-*c*] pyridin-4-
25 amine, quinolin-4-amine, tetrahydroquinolin-4-amine, naphthyridin-4-amine, and tetrahydronaphthyridin-4-amine compounds as well as certain analogous thiazolo and oxazolo compounds were synthesized and found to be useful as immune response modifiers, rendering them useful in the treatment of a variety of disorders.

30 There continues to be interest in and a need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other mechanisms.

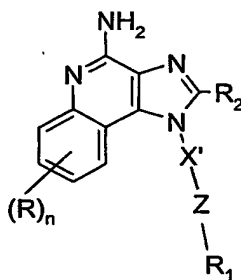
SUMMARY

The present invention provides a new class of compounds that are useful in inducing cytokine biosynthesis in animals. Such compounds are of the following Formula (I):



(I)

and more specifically of the following Formula (II):



(II)

wherein: R , n , R'' , R_1 , R_2 , X' , and Z are as defined below.

The compounds of Formulas I and II are useful as immune response modifiers (IRMs) due to their ability to induce cytokine biosynthesis (e.g., induce the biosynthesis or production of one or more cytokines) and otherwise modulate the immune response when administered to animals. The compounds are useful in the treatment of a variety of conditions such as viral diseases, and neoplastic diseases that are responsive to such changes in the immune response.

In another aspect, the present invention provides pharmaceutical compositions containing the immune response modifier compounds, and methods of inducing cytokine biosynthesis in an animal, treating a viral disease in an animal, and treating a neoplastic

disease in an animal, by administering an effective amount of one or more compounds of Formula I (and more specifically, of Formula II) and/or pharmaceutically acceptable salts thereof to the animal.

In another aspect, the invention provides methods of synthesizing compounds of Formulas I and II and intermediates useful in the synthesis of these compounds.

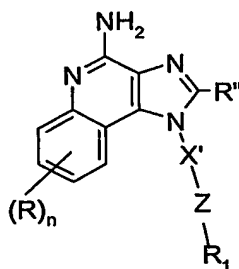
As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably.

The terms "comprising" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. Guidance is also provided herein through lists of examples, which can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

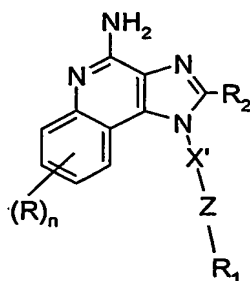
DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

The present invention provides a new class of compounds that are useful in inducing cytokine biosynthesis in animals. Such compounds are of the following Formula (I):



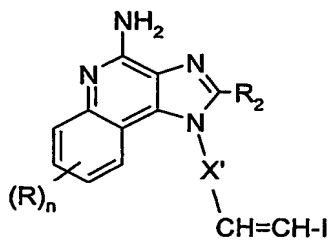
(I)

and more specifically of the following Formula (II):



(II)

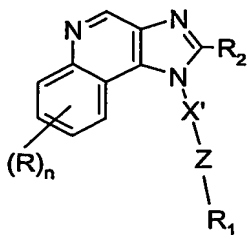
as well as intermediates for the preparation of compounds of Formulas (I) and (II),
 5 wherein the intermediates are of the following Formulas (III) and (IV):



(III)

10

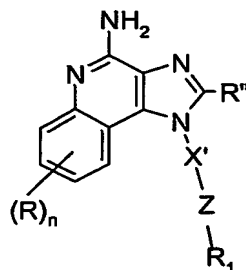
and



(IV)

15 wherein: R, n, R'', R₁, R₂, X', and Z are as defined below.

In one embodiment, the present invention provides compounds of the following
 Formula (I):



(I)

wherein:

- 5 Z is -CH=CH- or -C≡C-;
 X' is -CH(R₃)-, -CH(R₃)-alkylene-, or -CH(R₃)-alkenylene-;
 R₁ is selected from the group consisting of:
 -Ar,
 -Ar'-Y-R₄,
 10 -Ar'-X-Y-R₄, and
 -Ar'-R₅;

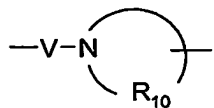
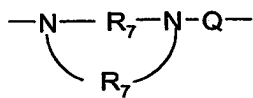
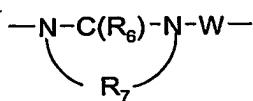
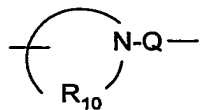
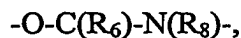
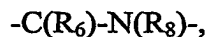
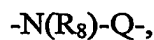
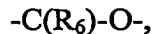
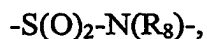
Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy,
 15 hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents
 20 independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

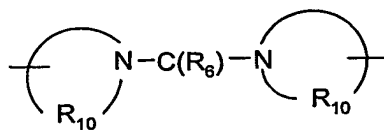
X is selected from the group consisting of alkylene, alkenylene, alkynylene,
 25 arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene,

or heterocyclylene, and wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:



, and



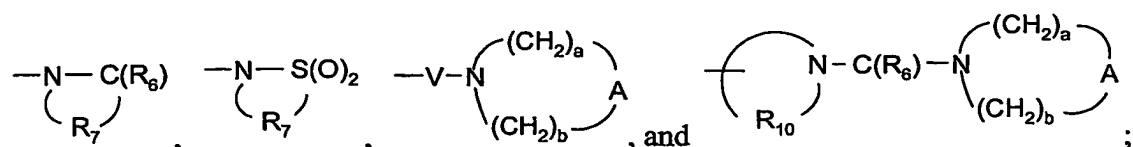
;

R₃ is hydrogen or C₁₋₁₀ alkyl;

R₄ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups

can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of



R₆ is selected from the group consisting of =O and =S;

R₇ is C₂₋₇ alkylene;

R₈ is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R₉ is selected from the group consisting of hydrogen and alkyl;

R₁₀ is C₃₋₈ alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)₀₋₂-, -CH₂-, and -N(R₄)-;

Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, and -C(R₆)-N(OR₉)-;

V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and -S(O)₂-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-;

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7 ;

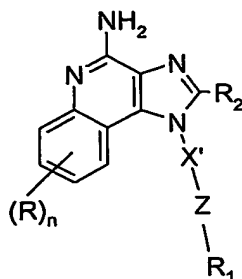
R is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl; and

n is 0 or 1;

R" is hydrogen or a non-interfering substituent;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention also provides compounds of the following Formula II:



(II)

wherein:

Z is $-\text{CH}=\text{CH}-$ or $-\text{C}\equiv\text{C}-$;

5 X' is $-\text{CH}(\text{R}_3)-$, $-\text{CH}(\text{R}_3)-\text{alkylene}-$, or $-\text{CH}(\text{R}_3)-\text{alkenylene}-$;

R₁ is selected from the group consisting of:

-Ar,

-Ar'-Y-R₄,

-Ar'-X-Y-R₄, and

10 -Ar'-R₅;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

15 Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

R₂ is selected from the group consisting of:

-R₄,

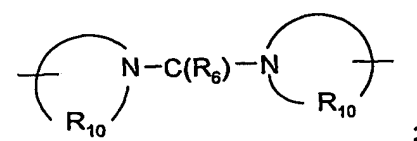
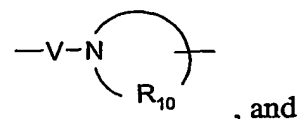
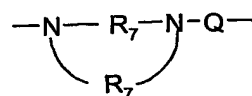
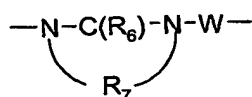
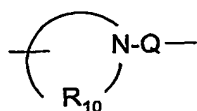
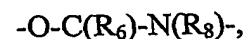
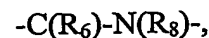
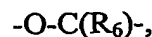
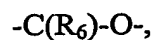
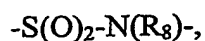
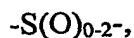
25 -X-R₄,

-X-Y-R₄, and

-X-R₅;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

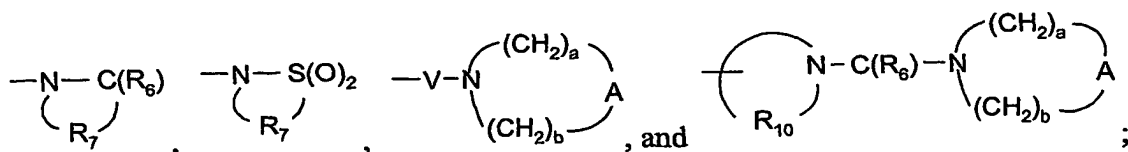


R_3 is hydrogen or C_{1-10} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl,

heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

10 R_5 is selected from the group consisting of



R₆ is selected from the group consisting of =O and =S;

R₇ is C₂₋₇ alkylene;

R₈ is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and aryl;

R_0 is selected from the group consisting of hydrogen and alkyl;

R₁₀ is C₃₋₈ alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)₀₋₂-, -CH₂- and -N(R₄)-;

20 Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, and -C(R₆)-N(OR₉)-;

V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and -S(O)₂-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-;

25 a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$;

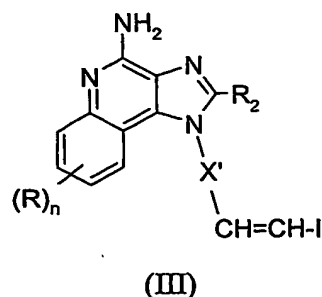
R is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl; and

n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides compounds, which are useful, for example, in preparing compounds of Formulas I and II.

In one embodiment, the present invention provides compounds of Formula III:



wherein:

X' is -CH(R₃)-, -CH(R₃)-alkylene-, or -CH(R₃)-alkenylene-;

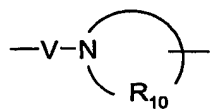
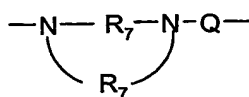
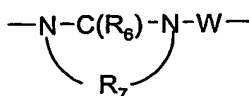
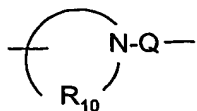
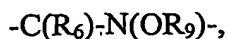
R₂ is selected from the group consisting of:

- R₄,
- X-R₄,
- X-Y-R₄, and
- X-R₅;

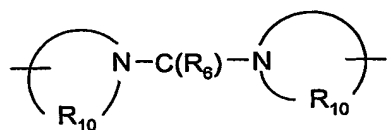
X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

- S(O)₀₋₂-,
- S(O)₂-N(R₈)-,
- C(R₆)-,
- C(R₆)-O-,
- O-C(R₆)-,
- O-C(O)-O-,
- N(R₈)-Q-,
- C(R₆)-N(R₈)-,
- O-C(R₆)-N(R₈)-,



, and



•

R₃ is hydrogen or C₁₋₁₀ alkyl;

R₄ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl,

heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl,

heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected

from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen,

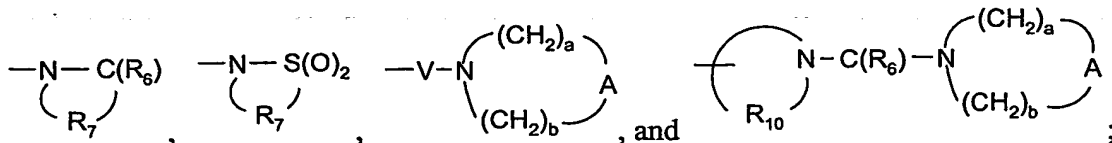
nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy,

heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino,

(dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl,

OXO;

R_5 is selected from the group consisting of



R₆ is selected from the group consisting of =O and =S;

R₇ is C₂₋₇ alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

5 A is selected from the group consisting of -O-, -C(O)-, -S(O)₀₋₂-, -CH₂-, and -N(R_4)-;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)₂-, -C(R_6)-N(R_8)-W-, -S(O)₂-N(R_8)-, -C(R_6)-O-, and -C(R_6)-N(OR₉)-;

10 V is selected from the group consisting of -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and -S(O)₂-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-;

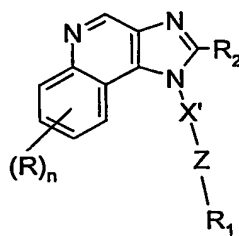
a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$;

R is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl; and

15 n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides compounds of the Formula IV:



(IV)

wherein:

Z is -CH=CH- or -C≡C-;

X' is -CH(R_3)-, -CH(R_3)-alkylene-, or -CH(R_3)-alkenylen-;

25 R_1 is selected from the group consisting of:

-Ar,

-Ar'-Y- R_4 ,

-Ar'-X-Y- R_4 , and

-Ar'-R₅;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

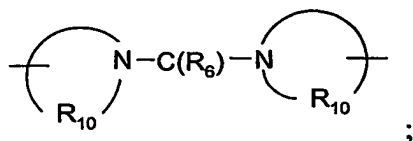
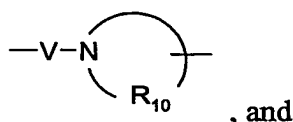
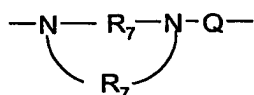
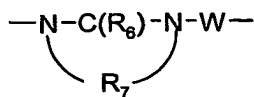
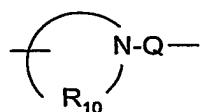
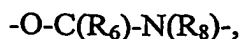
R₂ is selected from the group consisting of:

-R₄,
 -X-R₄,
 -X-Y-R₄, and
 -X-R₅;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

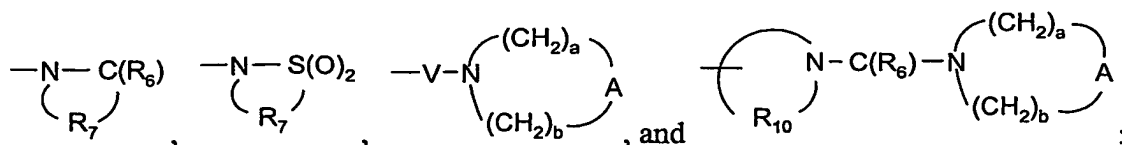
-S(O)₀₋₂-,
 -S(O)₂-N(R₈)-,
 -C(R₆)-,
 -C(R₆)-O-,
 -O-C(R₆)-,
 -O-C(O)-O-,
 -N(R₈)-Q-,
 -C(R₆)-N(R₈)-,



R_3 is hydrogen or C_{1-10} alkyl;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of



R_6 is selected from the group consisting of $=O$ and $=S$;

R₇ is C₂₋₇ alkylene;

R₈ is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R₉ is selected from the group consisting of hydrogen and alkyl;

5 R₁₀ is C₃₋₈ alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)₀₋₂-, -CH₂-, and -N(R₄)-;

Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, and -C(R₆)-N(OR₉)-;

10 V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and -S(O)₂-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

15 R is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl; and

n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

As used herein, the terms "alkyl," "alkenyl," "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e. cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene," "alkenylene," and "alkynylene" are the divalent forms of the "alkyl," "alkenyl," and "alkynyl" groups defined above. The terms, "alkylenyl," "alkenylenyl," and "alkynylenyl" are used when "alkylene," "alkenylene," and "alkynylene," respectively, are substituted. For example, an arylalkylenyl group comprises an alkylene moiety to which an aryl group is attached.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-." Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

5 The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

Unless otherwise indicated, the term "heteroatom" refers to the atoms O, S, or N.

10 The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

15 The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, 20 quinuclidinyl, homopiperidinyl (azepanyl), homopiperazinyl (diazepanyl), 1,3-dioxolanyl, aziridinyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, and the like. When "heterocyclyl" contains a nitrogen atom, the point of attachment of the heterocyclyl group may be the nitrogen atom.

25 The terms "arylene," "heteroarylene," and "heterocyclylene" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. The terms, "arylenyl," "heteroarylenyl," and "heterocyclenyl" are used when "arylene," "heteroarylene," and "heterocyclylene," respectively, are substituted. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

30 Herein, "non-interfering" means that the ability of the compound or salt, which includes a non-interfering substituent, to modulate the biosynthesis of one or more cytokines is not destroyed by the non-interfering substituent. For certain embodiments,

R" is hydrogen or a non-interfering substituent. Illustrative non-interfering R" groups include those described above for R₂.

When a group (or substituent or variable) is present more than once in any Formula described herein, each group (or substituent or variable) is independently selected, whether explicitly stated or not. For example, when an R₁ and an R₂ group both contain an R₄ group, each R₄ group is independently selected.

The invention is inclusive of the compounds described herein in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), salts, solvates, polymorphs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers. It should be understood that the term "compound" includes any or all of such forms, whether explicitly stated or not (although at times, "salts" are explicitly stated).

For any of the compounds presented herein, each one of the following variables (e.g., R, n, R", R₁, R₂, X', and Z, and so on) in any of its embodiments can be combined with any one or more of the other variables in any of their embodiments and associated with any one of the formulas described herein, as would be understood by one of skill in the art. Each of the resulting combinations of variables is an embodiment of the present invention.

For certain embodiments, R is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl.

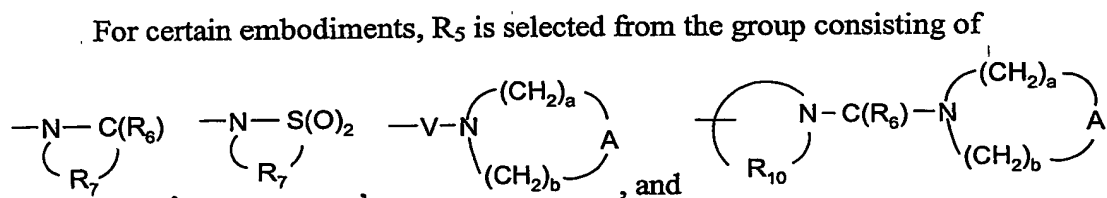
For certain embodiments, R₁ is selected from the group consisting of -Ar, -Ar'-Y-R₄, -Ar'-X-Y-R₄; and -Ar'-R₅. For certain embodiments, particularly embodiments of Formula II, R₁ is -Ar. In other embodiments, particularly embodiments of Formula II, R₁ is selected from the group consisting of 2-pyridinyl, 3-pyridinyl, and phenyl wherein the phenyl group can be unsubstituted or substituted by alkoxy, haloalkyl, halogen, nitro, or cyano. For certain embodiments, R₁ is phenyl, 3-chlorophenyl, 4-chlorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-pyridinyl, or 3-pyridinyl.

For certain embodiments, R" is hydrogen or a non-interfering substituent. Illustrative non-interfering R" groups include those described above for R₂.

For certain embodiments, R_2 is selected from the group consisting of $-R_4$, $-X-R_4$, $-X-Y-R_4$, and $-X-R_5$. For certain embodiments, particularly embodiments of Formula II, R_2 is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl. For certain embodiments, particularly embodiments of Formula II, n is 0 and R_2 is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl. For certain embodiments, particularly embodiments of Formula II, R_2 is selected from the group consisting of methyl, ethyl, propyl, butyl, ethoxymethyl, and 2-methoxyethyl.

For certain embodiments, R_3 is hydrogen or C_{1-10} alkyl.

For certain embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo.



For certain embodiments, R_6 is selected from the group consisting of $=O$ and $=S$.

For certain embodiments, R_7 is C_{2-7} alkylene.

For certain embodiments, R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl.

For certain embodiments, R_9 is selected from the group consisting of hydrogen and alkyl.

For certain embodiments, R_{10} is C_{3-8} alkylene.

For certain embodiments, A is selected from the group consisting of $-O-$, $-C(O)-$, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$.

For certain embodiments, Q is selected from the group consisting of a bond, -C(R₆)-, -C(R₆)-C(R₆)-, -S(O)₂-, -C(R₆)-N(R₈)-W-, -S(O)₂-N(R₈)-, -C(R₆)-O-, and -C(R₆)-N(OR₉)-.

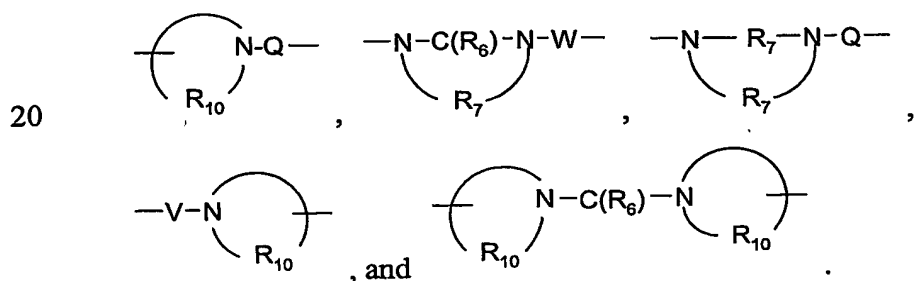
For certain embodiments, V is selected from the group consisting of -C(R₆)-, -O-C(R₆)-, -N(R₈)-C(R₆)-, and -S(O)₂-.

For certain embodiments, W is selected from the group consisting of a bond, -C(O)-, and -S(O)₂-.

For certain embodiments, X' is -CH(R₃)-, -CH(R₃)-alkylene-, or -CH(R₃)-alkenylene-. For certain embodiments, particularly of Formula II, X' is selected from the group consisting of -CH₂-C(CH₃)₂-, methylene, and propylene. For certain embodiments, X' is selected from the group consisting of -CH₂-, -(CH₂)₂-, and -(CH₂)₃-.

For certain embodiments, X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted by one or more -O- groups.

For certain embodiments, Y is selected from the group consisting of -S(O)_{0.2}-, -S(O)₂-N(R₈)-, -C(R₆)-, -C(R₆)-O-, -O-C(R₆)-, -O-C(O)-O-, -N(R₈)-Q-, -C(R₆)-N(R₈)-, -O-C(R₆)-N(R₈)-, -C(R₆)-N(OR₉)-,



For certain embodiments, Z is -CH=CH- or -C≡C-. For some embodiments, particularly embodiments of Formula II, Z is -C≡C-. In other embodiments, particularly of Formula II, Z is -CH=CH-.

For certain embodiments, Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl,

aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino.

For certain embodiments, Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino.

For certain embodiments, a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$.

For certain embodiments, n is 0 or 1. For certain embodiments, n is 0.

Preparation of the Compounds

Compounds of the invention can be prepared according to Reaction Scheme I, wherein R, R₁, R₂, X', and n are as defined above. In step (1) of Reaction Scheme I, an alkynyl amine of Formula $\text{HC}\equiv\text{C}-\text{X}'-\text{NH}_2$ is added to a 4-chloro-3-nitroquinoline of Formula V to afford an alkynyl-substituted 3-nitroquinolin-4-amine of Formula VI. The reaction is conveniently carried out by combining the alkynyl amine of Formula $\text{HC}\equiv\text{C}-\text{X}'-\text{NH}_2$ with a quinoline of Formula V in the presence of a base such as triethylamine in a suitable solvent such as dichloromethane or tetrahydrofuran. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods. Some amines of Formula $\text{HC}\equiv\text{C}-\text{X}'-\text{NH}_2$, such as propargylamine, are commercially available; others can be prepared by known synthetic methods. Compounds of Formula V are known and can be prepared according to known methods. See, for example, U.S. Patent Nos. 4,689,338; 4,929,624; 5,268,376; 5,346,905; 5,389,640; and 5,756,747.

In step (2) of Reaction Scheme I, an alkynyl-substituted 3-nitroquinolin-4-amine of Formula VI is reduced to an alkynyl-substituted quinoline-3,4-diamine of Formula VII. The reduction of the nitro group is conveniently carried out by adding an aqueous solution of sodium dithionite to an alkynyl-substituted 3-nitroquinolin-4-amine of Formula VI in a suitable solvent such as ethanol. The reaction can be carried out at ambient temperature, and the product can be isolated by conventional methods.

In step (3) of Reaction Scheme I, a quinoline-3,4-diamine of Formula VII is treated with a carboxylic acid equivalent to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula VIII. Suitable carboxylic acid equivalents include orthoesters of Formula $R_2C(O\text{-alkyl})_3$, 1,1-dialkoxyalkyl alkanoates of Formula $R_2C(O\text{-alkyl})_2(O\text{-C(O)-alkyl})$, and acid chlorides of Formula $R_2C(O)Cl$. The selection of the carboxylic acid equivalent is determined by the desired substituent at R_2 . For example, triethyl orthopropionate will provide a compound where R_2 is ethyl, and trimethyl orthovalerate will provide a compound where R_2 is a butyl group. The reaction is conveniently carried out by adding the carboxylic acid equivalent to a quinoline-3,4-diamine of Formula VII in a suitable solvent such as toluene or pyridine. Optionally, catalytic pyridine hydrochloride can be added. The reaction is carried out at a temperature high enough to drive off alcohol or water formed during the reaction, for example, at the reflux temperature of the solvent.

Alternatively, step (3) can be carried out in two steps when an acid chloride of Formula $R_2C(O)Cl$ is used as the carboxylic acid equivalent. Part (i) of step (3) is conveniently carried out by adding the acid chloride to a solution of a quinoline-3,4-diamine of Formula VII in a suitable solvent such as dichloromethane or acetonitrile to afford an amide. Optionally, a tertiary amine such as triethylamine, pyridine, or 4-dimethylaminopyridine can be added. The reaction can be carried out at ambient temperature or at an elevated temperature. The amide product can be isolated and optionally purified using conventional techniques. Part (ii) of step (3) involves heating the amide prepared in part (i) to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula VIII. The reaction is conveniently carried out in a suitable solvent such as toluene at a temperature sufficient to drive off water formed during the reaction. The reaction can also be carried out in a solvent such as ethanol or methanol in the presence of a base such as triethylamine. The product can be isolated using conventional methods.

In step (4a) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinoline of Formula VIII is oxidized to provide a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula IX using a conventional oxidizing agent capable of forming *N*-oxides. The reaction is conveniently carried out by adding 3-chloroperoxybenzoic acid to a compound of Formula VIII in a solvent such as dichloromethane or chloroform. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

In step (5a) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula IX is aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula X. Step (5a) can be carried out by the activation of an *N*-oxide of Formula IX by conversion to an ester and then reacting the ester with an aminating agent. Suitable activating agents include alkyl- or arylsulfonyl chlorides such as benzenesulfonyl chloride, methanesulfonyl chloride, or *p*-toluenesulfonyl chloride. Suitable aminating agents include ammonia, in the form of ammonium hydroxide, for example, and ammonium salts such as ammonium carbonate, ammonium bicarbonate, and ammonium phosphate. The reaction is conveniently carried out by adding ammonium hydroxide to a solution of the *N*-oxide of Formula IX in a suitable solvent such as dichloromethane or chloroform and then adding *p*-toluenesulfonyl chloride. The reaction can be carried out at ambient temperature. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

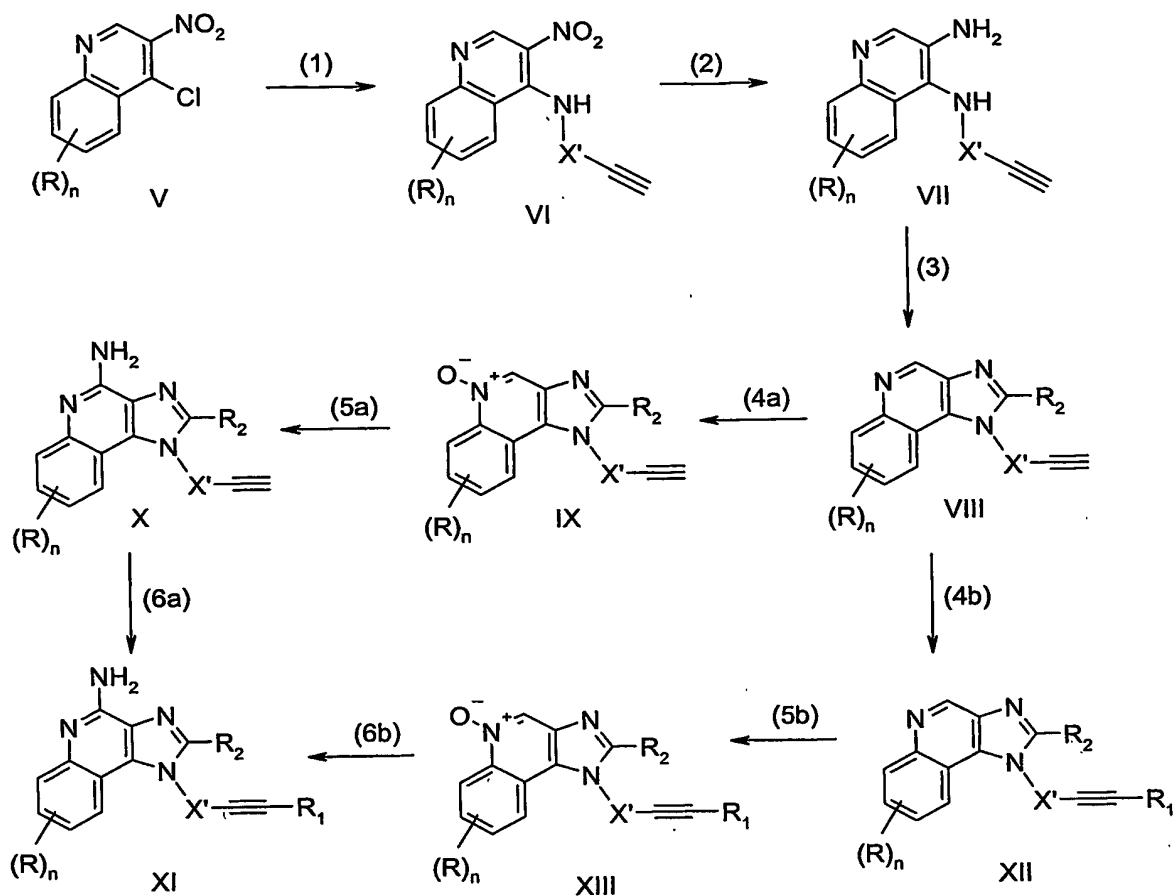
Steps (4a) and (5a) may also be carried out as a one-pot procedure by first adding 3-chloroperoxybenzoic acid to a 1*H*-imidazo[4,5-*c*]quinoline of Formula VIII in a solvent such as dichloromethane or chloroform. After the reaction is stirred for a period long enough to complete the oxidation, ammonium hydroxide and *p*-toluenesulfonyl chloride are sequentially added. The reaction can be carried out at ambient temperature, and the product of Formula X can be isolated using conventional methods.

In step (6a) of Reaction Scheme I, an alkynyl-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula X undergoes a Sonogashira coupling reaction with an aryl or heteroaryl iodide of Formula R₁-I to provide an arylalkynyl-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XI, a subgenus of Formula II. Numerous iodides of Formula R₁-I are commercially available; others can be prepared by known synthetic methods. The reaction is conveniently carried out by adding an iodide of Formula R₁-I to an alkynyl-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula X in the presence of catalytic amounts of copper (I) iodide and tris(dibenzylideneacetone)dipalladium(0) chloroform adduct and a base such as triethylamine. The coupling reaction is carried out in a suitable solvent such as *N,N*-dimethylformamide (DMF) at ambient temperature. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Steps (4a), (5a), and (6a) may also be carried out in a different order, as shown in steps (4b), (5b), and (6b) of Reaction Scheme I. In step (4b) of Reaction Scheme I, an alkynyl-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula VIII undergoes a Sonogashira coupling reaction with an aryl or heteroaryl iodide of Formula R₁-I to provide an
5 arylalkynyl-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XII, a subgenus of Formula IV. The reaction can be carried out as described in step (6a) above.

In steps (5b) and (6b) of Reaction Scheme I, an arylalkynyl-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XII is first oxidized to an arylalkynyl-substituted 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XIII, which is then aminated to provide an
10 arylalkynyl-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XI. Steps (5b) and (6b) can be carried out as described for steps (4a) and (5a) above. The product of Formula XI or a pharmaceutically acceptable salt thereof may be isolated using conventional methods.

Reaction Scheme I



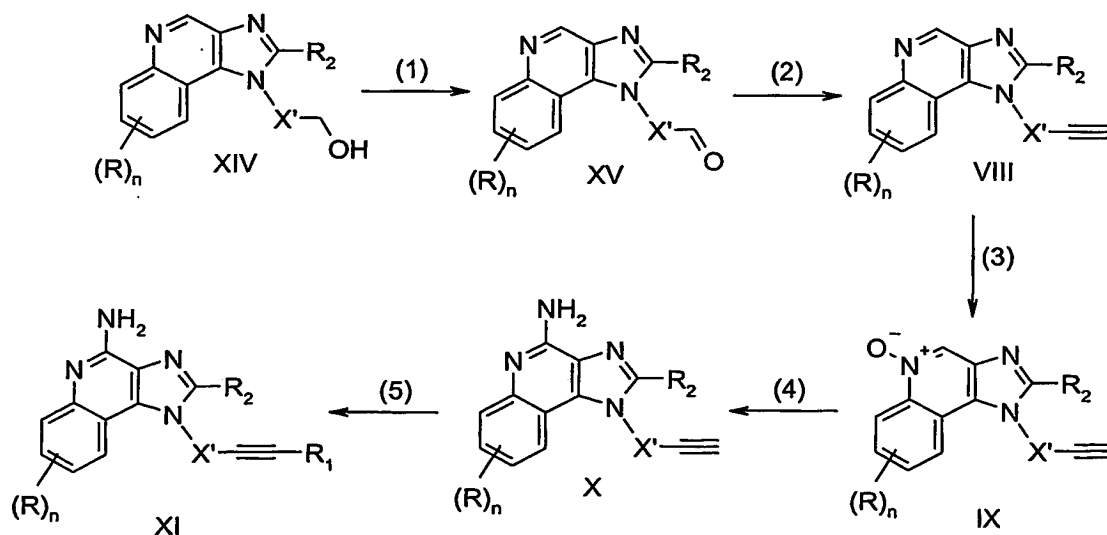
5 Compounds of the invention can also be prepared according to Reaction Scheme II, wherein R, R₁, R₂, X', and n are as defined above. In step (1) of Reaction Scheme II, a 1H-imidazo[4,5-c]quinolin-1-yl alcohol of Formula XIV is oxidized to provide an aldehyde-substituted 1H-imidazo[4,5-c]quinoline of Formula XV using conventional methods, for example, Swern oxidation conditions. Many compounds of Formula XIV are known; see for example, Gerster, U.S. Patent 4,689,338. Others can be readily prepared using known synthetic routes; see for example, Gerster et al., U.S. Patent 5,605,899 and Gerster, U.S. Patent 5,175,296. The Swern oxidation is conveniently carried out by adding a compound of Formula XIV followed by triethylamine to a mixture of oxalyl chloride and dimethylsulfoxide in a suitable solvent, such as dichloromethane. The reaction can be carried out at sub-ambient temperatures, such as -78 °C, and the product can be isolated using conventional methods.

In step (2) of Reaction Scheme II, an aldehyde-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XV is converted to an alkynyl-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula VIII. The reaction is conveniently carried out by adding diethyl 1-diazo-2-oxopropylphosphonate to the aldehyde-substituted 1*H*-imidazo[4,5-*c*]quinoline of
 5 Formula XV in the presence of a mild base such as potassium carbonate. The reaction is carried out in a suitable solvent such as dichloromethane at ambient temperature. The product can be isolated using conventional methods.

In steps (3) and (4) of Reaction Scheme II, an alkynyl-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula VIII is first oxidized to an alkynyl-substituted 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula IX, which is then aminated to provide an alkynyl-
 10 substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula X. Steps (3) and (4) are identical to steps (4a) and (5a) in Reaction Scheme I.

In step (5) of Reaction Scheme II an alkynyl-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula X is coupled with an aryl or heteroaryl iodide of Formula
 15 R₁-I to provide an arylalkynyl-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XI, a subgenus of Formula II. Step (5) is identical to step (6a) in Reaction Scheme I. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme II

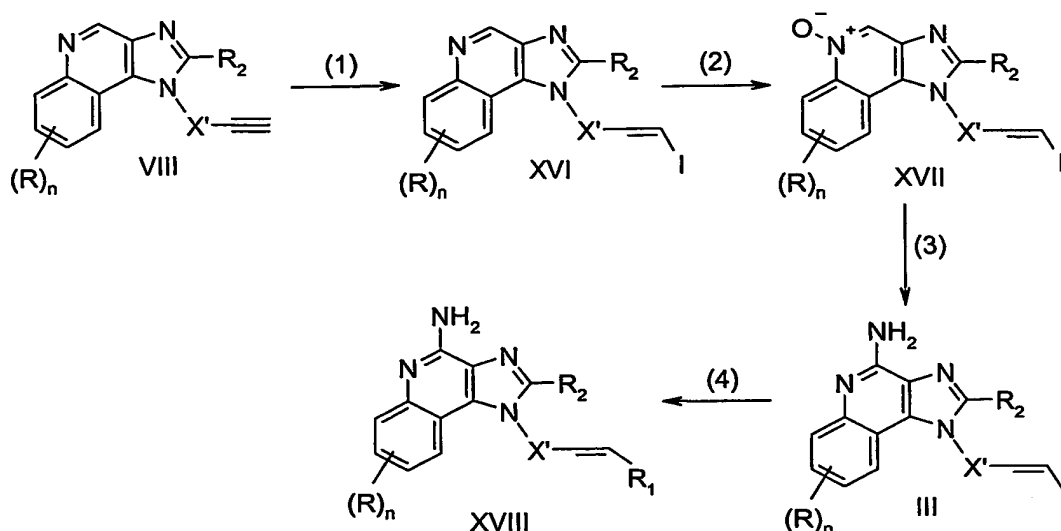


Arylalkenyl-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amines of the invention can be prepared according to Reaction Scheme III, wherein R, R₁, R₂, X', and n are as defined above. In step (1) of Reaction Scheme III, an alkynyl-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula VIII, prepared as described in Reaction Scheme I or Reaction Scheme II, is converted to a vinyl iodide of Formula XVI. The reaction can be carried out by hydrozirconation of the alkyne of Formula VIII and reaction of the resulting complex with iodine. The reaction is conveniently carried out by adding bis(cyclopentadienyl)zirconium chloride hydride (Schwartz's Reagent) to a solution of an alkynyl-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula VIII in a suitable solvent such as dichloromethane. The reaction can be carried out at a sub-ambient temperature such as 0 °C. Solid iodine is then added to the intermediate complex to provide the vinyl iodide of Formula XVI. The product can be isolated by conventional methods.

In steps (2) and (3) of Reaction Scheme III, an alkenyl-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XVI is first oxidized to an alkenyl-substituted 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XVII, which is then aminated to provide an alkenyl-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula III. Steps (2) and (3) of Reaction Scheme III can be carried out as described in steps (4a) and (5a) in Reaction Scheme I.

In step (4) of Reaction Scheme III, the vinyl iodide of Formula III is coupled with a boronic acid of Formula R₁-B(OH)₂, an anhydride thereof, or a boronic acid ester of Formula R₁-B(O-alkyl)₂ to provide an arylalkenyl-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XVIII, which is a subgenus of Formula II. The Suzuki coupling is carried out by combining a compound of Formula III with a boronic acid or an ester or anhydride thereof in the presence of palladium (II) acetate, triphenylphosphine, and a base such as sodium carbonate in a suitable solvent mixture such as water and ethanol. The reaction can be carried out at an elevated temperature (e.g., 70 °C). Many boronic acids of Formula R₁-B(OH)₂, anhydrides thereof, and boronic acid esters of Formula R₁-B(O-alkyl)₂ are commercially available; others can be readily prepared using known synthetic methods. See, for example, Li, W. et al, *J. Org. Chem.*, 67, 5394-5397 (2002). The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme III



Compounds of the invention can also be prepared using variations of the synthetic routes shown in Reaction Schemes I through III. For example, in Reaction Scheme III in those instances where R_1 is not susceptible to oxidation, the Suzuki coupling can be carried out prior to the oxidation and amination. Compounds of the invention can also be prepared using the synthetic routes described in the EXAMPLES below.

Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound or salt of the invention as described above in combination with a pharmaceutically acceptable carrier.

The terms "a therapeutically effective amount" and "effective amount" mean an amount of the compound or salt sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. Although the exact amount of active compound or salt used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound or salt, the nature of the carrier, and the intended dosing regimen, it is anticipated that the compositions of the invention will contain sufficient active ingredient to provide a dose of about 100

nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram (μ g/kg) to about 5 mg/kg, of the compound or salt to the subject. A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like.

The compounds or salts of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds or salts of the invention may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

Compounds or salts of the invention have been shown to induce the production of certain cytokines in experiments performed according to the test set forth below. These results indicate that the compounds or salts are useful as immune response modifiers that can modulate the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds or salts of the invention generally include interferon- α (IFN- α) and/or tumor necrosis factor- α (TNF- α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds or salts of the invention include IFN- α , TNF- α , IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds or salts useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. The animal to which the compound or salt or composition is administered for induction of cytokine biosynthesis may have a disease as described *infra*, for example a viral disease or a neoplastic disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, compounds or salts of the invention can affect other aspects of the innate immune response. For example,

natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds or salts may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, the compounds or salts may cause proliferation and differentiation of B-lymphocytes.

5 Compounds or salts of the invention can also have an effect on the acquired immune response. For example, the production of the T helper type 1 (T_H1) cytokine IFN- γ may be induced indirectly and the production of the T helper type 2 (T_H2) cytokines IL-4, IL-5 and IL-13 may be inhibited upon administration of the compounds or salts.

10 Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or salt or composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound or salt and other component or components may be administered separately; together but independently such as in a solution; or together and associated with one another such as
15 (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

 Conditions for which compounds or salts identified herein may be used as treatments include, but are not limited to:

20 (a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B
25 virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

30 (b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus *Escherichia*, *Enterobacter*, *Salmonella*, *Staphylococcus*, *Shigella*, *Listeria*, *Aerobacter*, *Helicobacter*, *Klebsiella*, *Proteus*, *Pseudomonas*, *Streptococcus*, *Chlamydia*, *Mycoplasma*, *Pneumococcus*, *Neisseria*, *Clostridium*, *Bacillus*, *Corynebacterium*, *Mycobacterium*, *Campylobacter*, *Vibrio*, *Serratia*, *Providencia*, *Chromobacterium*, *Brucella*, *Yersinia*, *Haemophilus*, or *Bordetella*;

(c) other infectious diseases, such chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases including but not limited to malaria, pneumocystis carinii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection;

5 (d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, leukemias including but not limited to myelogenous leukemia, chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers;

10 (e) T_H2 -mediated, atopic diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, and Ommen's syndrome;

(f) certain autoimmune diseases such as systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, discoid lupus, alopecia areata; and

15 (g) diseases associated with wound repair such as, for example, inhibition of keloid formation and other types of scarring (e.g., enhancing wound healing, including chronic wounds).

Additionally, compounds or salts of the present invention may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic
20 immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens, toxoids, toxins; self-antigens; polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; autologous vaccines; recombinant proteins; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B,
25 parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

30 Compounds or salts of the present invention may be particularly helpful in individuals having compromised immune function. For example, compounds or salts may be used for treating the opportunistic infections and tumors that occur after suppression of

cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

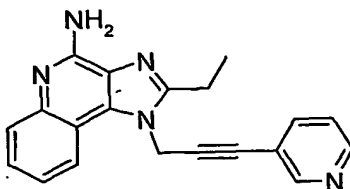
Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound or salt of the invention to the animal.

An amount of a compound or salt effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN- α , TNF- α , IL-1, IL-6, IL-10 and IL-12 that is increased (induced) over a background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μ g/kg to about 5 mg/kg. The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μ g/kg to about 5 mg/kg. An amount of a compound or salt effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μ g/kg to about 5 mg/kg.

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

EXAMPLES

Example 1

2-Ethyl-1-[3-(pyridin-3-yl)-2-propynyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine

5 Part A

Triethylamine (8.0 mL, 1.2 eq.) was added to a mixture of 4-chloro-3-nitroquinoline (10.0 g, 47.9 mmol, 1.0 eq.) in tetrahydrofuran (THF, 200 mL). Propargylamine (3.4 mL, 1.1 eq.) was added and the reaction mixture was stirred vigorously for 1.5 hours. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between chloroform (700 mL) and water (200 mL). The organic layer was washed with water (1 x 200 mL). The combined aqueous layers were back extracted with chloroform (2 x 150 mL). The combined organics were dried over magnesium sulfate and concentrated under reduced pressure to provide 10.59 g of 4-chloro-3-nitro-*N*-(2-propynyl)quinoline as a yellow solid.

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Part B

A solution of sodium dithionite (40.57 g of 85%, 5.0 eq.) in water (150 mL) was added over a period of 5 minutes to a vigorously stirred suspension of the material from Part A (10.59 g, 46.60 mmol, 1.0 eq.) in ethanol (460 mL). The reaction mixture was stirred for 20 minutes and then concentrated under reduced pressure. The residue was partitioned between chloroform (300 mL) and water (300 mL); the organic layer was separated. The aqueous layer was back extracted with additional chloroform. The combined organics were dried over magnesium sulfate and concentrated under reduced pressure to provide 3.06 g of *N*⁴-(2-propynyl)quinoline-3,4-diamine as a pale yellow solid (lot 1). A small amount of methanol was added to the aqueous layer in the separatory funnel to dissolve an oily yellow material coating the separatory funnel. The aqueous layer was extracted with chloroform (5 x 150 mL). The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure to provide 3.66 g of *N*⁴-(2-propynyl)quinoline-3,4-diamine as a yellow solid (lot 2). Analysis by NMR showed

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~80% purity. The aqueous layer was made basic (pH ~8) with aqueous saturated sodium bicarbonate and then extracted with chloroform (2 x 150 mL). The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure to provide *N*⁴-(2-propynyl)quinoline-3,4-diamine as a yellow oil, this material was combined with lot 2 for a total of 7.03 g.

Part C

A suspension of lot 1 (3.06 g, 15.5 mmol., 1.0 eq.) from Part B in a mixture of chloroform (15 mL) and toluene (135 mL) was warmed until most of the solid had gone into solution. Triethyl orthopropionate (3.4 mL, 1.1 eq) and pyridine hydrochloride (180 mg, 0.1 eq.) were added and the reaction mixture was heated at 110 °C for 1.5 hours. The reaction mixture was allowed to cool to ambient temperature and then concentrated under reduced pressure to provide crude product. The material from Part B lot 2 was cyclized using the same method. The combined crude products were purified by column chromatography (silica gel eluting with 10/90 methanol/chloroform) to provide 6.79 g of 2-ethyl-1-(2-propynyl)-1*H*-imidazo[4,5-*c*]quinoline as a light tan solid.

Part D

3-Chloroperoxybenzoic acid (1.21 g of 77%, 1.15 eq.) was added in a single portion to a solution of 2-ethyl-1-(2-propynyl)-1*H*-imidazo[4,5-*c*]quinoline (1.00 g, 4.25 mmol, 1.0 eq) in chloroform (42 mL). The reaction mixture was stirred at ambient temperature for 1 hour at which time analysis by thin layer chromatography (TLC) indicated that the reaction was complete. The reaction mixture was diluted with chloroform (150 mL) and washed with aqueous saturated sodium bicarbonate (2 x 50 mL). The combined aqueous layers were back extracted with chloroform (3 x 30 mL). The combined organics were dried over magnesium sulfate and concentrated under reduced pressure to provide 1.19 g of 2-ethyl-1-(2-propynyl)-1*H*-imidazo[4,5-*c*]quinoline 5-oxide as a white solid.

Part E

Ammonium hydroxide (43 mL) was added to a stirred suspension of the material from Part D in chloroform (43 mL). Tosyl chloride (0.89 g, 1.1 eq) was added and the

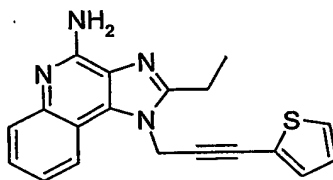
reaction mixture was stirred vigorously for 2 hours. The reaction mixture was diluted with chloroform (30 mL) and the layers were separated. The aqueous layer was back extracted with chloroform (2 x 20 mL). The combined organics were dried over magnesium sulfate and concentrated under reduced pressure to provide a brown solid. This material was
5 trituated with ethyl acetate (~20 mL), isolated by filtration, rinsed with ethyl acetate (3 x 7 mL) and dried under vacuum at 70 °C to provide 884 mg of an off white solid. This material was trituated with warm diethyl ether (15 mL), isolated by filtration, rinsed with diethyl ether (2 x 10 mL) to provide 857 mg of product. This material was recrystallized twice from dichloroethane (~40 mL) and dried under vacuum at 80 °C to provide 512 mg
10 of 2-ethyl-1-(2-propynyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as off-white crystals, mp 182-184°C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.20 (dd, *J*=1.0, 8.2 Hz, 1H), 7.61 (dd, *J*=1.0, 8.3 Hz, 1H), 7.43 (ddd, *J*=1.3, 7.0, 8.3 Hz, 1H), 7.26 (ddd, *J*=1.3, 7.0, 8.2 Hz, 1H), 6.49 (s, 2H), 5.42 (d, *J*=2.4 Hz, 2H), 3.51 (t, *J*=2.4 Hz, 1H), 2.99 (q, *J*=7.5 Hz, 2H), 1.37 (t, *J*=7.5 Hz, 3H); MS (APCI *m/z* 251 (*M* + *H*)⁺; Anal. calcd for C₁₅H₁₄N₄•0.01 C₂H₄Cl₂•0.03 H₂O: C, 71.64; H, 5.64; N, 22.25. Found: C, 71.28; H, 5.63; N, 22.41. Karl
15 Fischer (KF): 0.20.

Part F

Tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (54.6 mg, 0.03 eq.),
20 3-iodopyridine (425 mg, 1.1 eq.), triethylamine (735 µL, 3.0 eq.), and copper (I) iodide (20.1 mg, 0.06 eq.) were added sequentially to a solution of 2-ethyl-1-(2-propynyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (440 mg, 1.76 mmol, 1.0 eq.) in *N,N*-dimethylformamide (DMF, 18 mL). The reaction mixture was stirred at ambient temperature for 1 hour at which time analysis by ¹H NMR showed that the reaction was complete. The reaction
25 mixture was concentrated under reduced pressure and the residue purified by column chromatography (20 g of silica gel eluting with 10/90 methanol/chloroform) to provide 0.8 g of a light yellow solid. This material was trituated with water (~20 mL), isolated by filtration, rinsed with water (2 x 5 mL) and dried to give 0.50 g of tan solid. The solid was suspended in water (~10 mL), then made basic (pH ~11) with 10% aqueous sodium
30 hydroxide, isolated by filtration, rinsed with water, and then trituated with methanol. The resulting material was dissolved in warm 10/90 methanol/chloroform (40 mL), absorbed onto silica gel (2 g) and eluted with 10/90 methanol/chloroform. The eluant was allowed

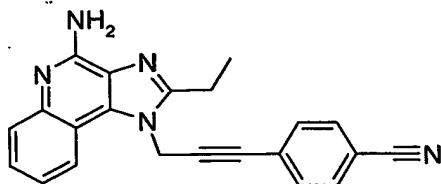
to dry at ambient temperature overnight and then the residue was dried under vacuum at 80 °C overnight to provide 260 mg of 2-ethyl-1-[3-(pyridin-3-yl)-2-propynyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine hydroiodide as an off white powder, mp 249-251°C (dec.). ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.24 (br s, 1H), 8.74 (br s, 2H), 8.54 (m, 3H), 7.86 (d, *J*=7.6 Hz, 1H), 7.78 (m, 2H), 7.65 (ddd, *J*=1.0, 8.2, 8.2 Hz, 1H), 7.39 (ddd, *J*=0.6, 4.9, 7.9 Hz, 1H), 5.86 (s, 2H), 3.14 (q, *J*=7.5 Hz, 2H), 1.44 (t, *J*=7.5 Hz, 3H); MS (APCI) *m/z* 328 (M + H)⁺; Anal. calcd for C₂₀H₁₇N₅•HI•0.02CHCl₃: C, 52.54; H, 3.97; N, 15.30. Found: C, 52.68; H, 3.92; N, 15.25.

Example 2

2-Ethyl-1-[3-(thien-2-yl)-2-propynyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine

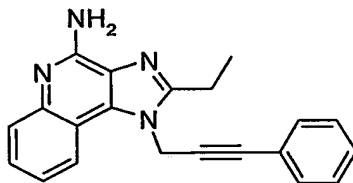
Tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (62.1 mg, 0.03 eq.), 2-iodothiophene (0.46 g, 1.1 eq.), triethylamine (0.61 g, 3 eq.), and copper (I) iodide (23 mg, 0.06) were added sequentially to a solution of 2-ethyl-1-(2-propynyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.5 g, 2.0 mmol, 1.0 eq) in DMF. The reaction mixture was stirred at ambient temperature for 3.5 hours. The reaction mixture was concentrated under reduced pressure to provide crude product which was purified by column chromatography (silica gel eluting with 5/95 methanol/dichloromethane). The residue was purified by recrystallization from 1,2-dichloroethane to provide 50 mg of 2-ethyl-1-[3-(thien-2-yl)-2-propynyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine hydroiodide as brown powder, mp 185-205° C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.24 (s, 1H), 8.80 (br, 2H), 8.47 (dd, *J*=0.9, 8.1 Hz, 1H), 7.86 (dd, *J*=1.0, 8.4 Hz, 1H), 7.74 (ddd, *J*=1.1, 7.2, 8.3 Hz, 1H), 7.64 (ddd, *J*=1.1, 7.2, 8.3 Hz, 1H), 7.61 (dd, *J*=1.1, 5.0 Hz, 1H), 7.27 (dd, 1.2, 3.7 Hz, 1H), 7.05 (dd, *J*= 3.5, 5.1 Hz, 1H), 5.84 (s, 2H), 3.12 (q, *J*=7.4 Hz, 2H), 1.42 (t, *J*=7.4 Hz, 3H); MS (APCI) *m/z* 333 (M + H)⁺; Anal. calcd for C₁₉H₁₆N₄S•HI: C, 49.59; H, 3.72; N, 12.17. Found: C, 49.86; H, 3.64; N, 12.23.

Example 3

4-[3-(4-Amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-propynyl]benzonitrile

5 Tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (62.1 mg, 0.03 eq.), 4-iodobenzonitrile (0.50 g, .11 eq.), triethylamine (0.61 g, 3 eq.), and copper (I) iodide (23 mg, 0.06 eq.) were added sequentially to a solution of 2-ethyl-1-(2-propynyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.5 g, 2.0 mmol, 1.0 eq) in DMF. The reaction mixture was stirred at ambient temperature for 3.5 hours. The reaction mixture was concentrated under reduced pressure to provide crude product which was purified by column chromatography (silica gel eluting with 5/95 methanol/dichloromethane). The residue was purified by recrystallization from 1,2-dichloroethane to provide 60 mg of 4-[3-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-propynyl]benzonitrile hydroiodide as a brown powder, mp 180-241°C (dec). ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.23 (br s, 1H), 8.47 (d, J=8.1 Hz, 1H), 8.44 (br, 2H), 7.82 (m, 3H), 7.69 (t, J=7.2 Hz, 1H), 7.60 (t, J=7.1 Hz, 1H), 7.54 (d, J=8.7 Hz, 2H), 5.84 (s, 2H), 3.13 (q, J=7.4 Hz, 2H), 1.42 (t, J=7.4 Hz, 3H); MS *m/z* 352 (M + H)⁺; Anal. calcd for C₂₂H₁₇N₅•HI•0.09 1,2-dichloroethane: C, 54.50; H, 3.79; N, 14.33. Found: C, 54.54; H, 3.59; N, 14.26.

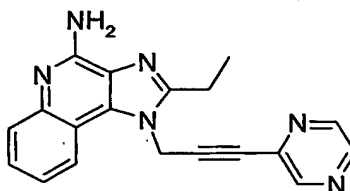
Example 4

2-Ethyl-1-(3-phenyl-2-propynyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine

25 Tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (62.1 mg, 0.03 eq.), 4-iodobenzene (0.45 g, 1.1 eq.), triethylamine (0.61 g, 3 eq.), and copper (I) iodide (23 mg, 0.06 eq.) were added sequentially to a solution of 2-ethyl-1-(2-propynyl)-1*H*-

imidazo[4,5-*c*]quinolin-4-amine (0.5 g, 2.0 mmol, 1.0 eq) in DMF. The reaction mixture was stirred at ambient temperature overnight. The reaction mixture was concentrated under reduced pressure to provide crude product which was purified by column chromatography (silica gel eluting with 8/92 methanol/dichloromethane). The residue was purified by recrystallization from 1,2-dichloroethane to provide 60 mg of 2-ethyl-1-(3-phenyl-2-propynyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine hydroiodide as a brown powder, mp 200-212°C (dec). ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.25 (s, 1H), 8.79 (br, 2H), 8.53 (dd, *J*=0.9, 8.5 Hz, 1H), 7.86 (dd, *J*=0.9, 8.3 Hz, 1H), 7.74 (ddd, *J*=1.2, 7.2, 8.4 Hz, 1H), 7.66 (ddd, *J*=1.2, 7.2, 8.3 Hz, 1H), 7.36 (m, 5H), 5.82 (s, 2H), 3.15 (q, *J*=7.5 Hz, 2H), 1.43 (t, *J*=7.5 Hz, 3H); MS (APCI) *m/z* 327 (*M* + *H*)⁺; Anal. Calcd for C₂₁H₁₈N₄•HI: C, 55.52; H, 4.22; N, 12.33. Found: C, 55.80; H, 3.94; N, 12.46.

Example 5

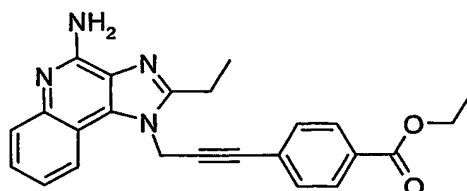
2-Ethyl-1-[3-(pyrazin-2-yl)-2-propynyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine

Tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (0.12 mg, 0.03 eq.), 2-iodopyrazine (0.90 g, 1.1 eq), triethylamine (1.21 g, 3 eq.), and copper (I) iodide (46 mg, 0.06 eq.) were added sequentially to a solution of 2-ethyl-1-(2-propynyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1 g, 4 mmol, 1.0 eq.) in DMF. The reaction mixture was stirred at ambient temperature overnight. The reaction mixture was concentrated under reduced pressure to provide crude product which was purified by column chromatography (silica gel eluting with 8/92 methanol/dichloromethane). The residue was purified by recrystallization from DMF to provide 100 mg of 2-ethyl-1-[3-(pyrazin-2-yl)-2-propynyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine hydroiodide as tan granules, mp 180-225°C (dec). ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.31 (s, 1H), 8.70 (br s, 2H), 8.68 (d, *J* = 1.4 Hz, 1H), 8.61 (m, 2H), 8.48 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.73 (m, 1H), 7.62 (m, 1H), 5.93 (s, 2H), 3.14 (q, *J* = 7.4 Hz, 2H), 1.43 (t, *J* = 7.4 Hz, 3H); MS (APCI) *m/z*

329 (M + H)⁺; Anal. calcd. for C₁₉H₁₆N₆•HI•0.06 DMF: C, 50.01; H, 3.81; N, 18.43.
Found: C, 49.96; H, 3.84; N, 18.15.

Example 6

5 Ethyl 4-[3-(4-Amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-propynyl]benzoate



Part A

10 Tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (65.9 mg, 0.03 eq.), ethyl 4-iodobenzoate (388 μ L, 1.1 eq.), triethylamine (887 μ L, 3.0 eq.), and copper (I) iodide (24.2 mg, 0.06 eq.) were added sequentially to a solution of 2-ethyl-1-(2-propynyl)-1*H*-imidazo[4,5-*c*]quinoline (499 mg, 2.12 mmol, 1.0 eq.) in DMF (10.6 mL). The reaction mixture was stirred at ambient temperature for 1 hour and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel eluting with 5/95 methanol/chloroform) to provide 0.70 g of ethyl 4-[3-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-propynyl]benzoate as a light tan solid.

Part B

20 3-Chloroperoxybenzoic acid (0.54 g of 77%, 1.15 eq.) was added in a single portion to a solution of the material from Part A in chloroform (18 mL). The reaction mixture was stirred at ambient temperature for 1.5 hour. The reaction mixture was diluted with chloroform (100 mL), washed with aqueous saturated sodium bicarbonate (2 x 30 mL), dried over magnesium sulfate and concentrated under reduced pressure to provide 0.70 g of ethyl 4-[3-(2-ethyl-5-oxy-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-propynyl]benzoate as a white solid.

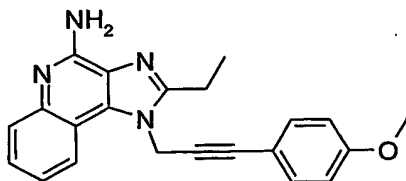
Part C

Ammonium hydroxide (15 mL) was added to a stirred solution of the material from Part B in chloroform (15 mL). Tosyl chloride (0.37 g, 1.1 eq) was added and the reaction

mixture was stirred vigorously for 4 hours. The reaction mixture was diluted with chloroform (30 mL) and the layers were separated. The aqueous layer was back extracted with chloroform (2 x 20 mL). The combined organics were dried over magnesium sulfate and concentrated under reduced pressure to provide 0.77 g of a light brown solid. This material was triturated with ethyl acetate (10 mL), isolated by filtration and rinsed with ethyl acetate (2 x 5 mL) to provide 512 mg of a tan solid. This solid was slurried with warm 9/1 acetonitrile/chloroform (~30 mL), cooled to ambient temperature, isolated by filtration and dried under vacuum at 80 °C to provide 0.40 g of ethyl 4-[3-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-propynyl]benzoate as a white powder, mp 221-222°C (dec). ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.31 (d, *J*=0.8, 8.1 Hz, 1H), 7.89 (d, *J*=8.5 Hz, 2H), 7.62 (dd, *J*=1.0, 8.3 Hz, 1H), 7.49 (d, *J*=8.5 Hz, 2H), 7.44 (m, 1H), 7.29 (ddd, *J*=1.3, 7.6, 7.6 Hz, 1H), 6.51 (s, 2H), 5.73 (s, 2H), 4.28 (q, *J*=7.1 Hz, 2H), 3.06 (q, *J*=7.5 Hz, 2H), 1.41 (t, *J*=7.5 Hz, 3H), 1.29 (t, *J*=7.1 Hz, 3H); MS (APCI) *m/z* 399 (M+H)⁺; Anal. Calc. for C₂₄H₂₂N₄O₂•0.06 CHCl₃: C, 71.24; H, 5.48; N, 13.81. Found: C, 71.02; H, 5.36; N, 13.72.

Example 7

2-Ethyl-1-[3-(4-methoxyphenyl)-2-propynyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

Tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (64 mg, 0.03 eq.), 4-iodoanisole (531 mg, 1.1 eq.), triethylamine (862 μL, 3.0 eq.), and copper (I) iodide (23.6 mg, 0.06 eq.) were added sequentially to a solution of 2-ethyl-1-(2-propynyl)-1*H*-imidazo[4,5-*c*]quinoline (485 mg, 2.06 mmol, 1.0 eq.) in DMF (10 mL). The reaction mixture was stirred at ambient temperature for 3 hour and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel eluting with 2/98 methanol/chloroform) to provide 0.34 g of 2-ethyl-1-[3-(4-methoxyphenyl)-2-propynyl]-1*H*-imidazo[4,5-*c*]quinoline as a clear oil that partially crystallized on standing.

Part B

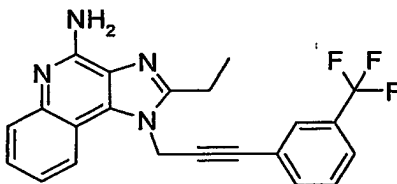
Using the method of Example 6 Part B, the material from Part A was oxidized to provide 0.32 g of 2-ethyl-1-[3-(4-methoxyphenyl)-2-propynyl]-1*H*-imidazo[4,5-
5 c]quinolin-5-oxide as a light yellow solid.

Part C

Using the method of Example 6 Part C, the material from Part B was aminated. The crude product was purified by column chromatography (silica gel eluting with 5/95
10 methanol/chloroform) followed by recrystallization from ethyl acetate to provide 126 mg of 2-ethyl-1-[3-(4-methoxyphenyl)-2-propynyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white powder, mp 179-181°C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.32 (dd, *J*=1.0, 8.2 Hz, 1H), 7.61 (dd, *J*=1.0, 8.3 Hz, 1H), 7.44 (ddd, *J*=1.4, 7.0, 8.3 Hz, 1H), 7.30 (m, 3H), 6.88 (m, 2H), 6.49 (s, 2H), 5.63 (s, 2H), 3.73 (s, 3H), 3.05 (q, *J*=7.5 Hz, 2H), 1.40 (t, *J*=7.5 Hz,
15 3H); MS (APCI) *m/z* 357 (M + H)⁺; Anal. calcd for C₂₂H₂₀N₄O•0.04 C₄H₈O₂•0.05 H₂O: C, 73.76; H, 5.70; N, 15.53. Found: C, 73.47; H, 5.60, N: 15.48; KF: 0.23.

Example 8

2-Ethyl-1-[3-(3-trifluoromethylphenyl)-2-propynyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

Tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (66 mg, 0.03 eq.), 3-iodobenzotrifluoride (336 μL, 1.1 eq.), triethylamine (889 μL, 3.0 eq.), and copper (I)
25 iodide (24.3 mg, 0.06 eq.) were added sequentially to a solution of 2-ethyl-1-(2-propynyl)-1*H*-imidazo[4,5-*c*]quinoline (500 mg, 2.13 mmol, 1.0 eq.) in DMF (10.6 mL). The reaction mixture was stirred at ambient temperature for 1 hour and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel

eluting with 2/98 methanol/chloroform) to provide 0.73 g of 2-ethyl-1-[3-(3-trifluoromethylphenyl)-2-propynyl]-1*H*-imidazo[4,5-*c*]quinoline as a light tan solid.

Part B

- 5 Using the method of Example 6 Part B, the material from Part A was oxidized to provide 0.69 g of 2-ethyl-1-[3-(3-trifluoromethylphenyl)-2-propynyl]-1*H*-imidazo[4,5-*c*]quinoline-5-oxide as a light tan solid.

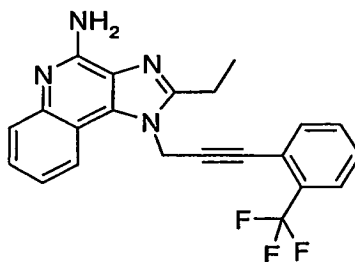
Part C

- 10 Using the method of Example 6 Part C, the material from Part B was aminated. The crude product was purified by trituration with diethyl ether to provide 453 mg of an off white solid. This material was recrystallized sequentially from isopropanol, ethanol, and ethyl acetate to provide 192 mg of 2-ethyl-1-[3-(3-trifluoromethylphenyl)-2-propynyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white powder, mp 202.5-203.5°C. ¹H
- 15 NMR (300 MHz, DMSO-*d*₆) δ 8.32 (dd, *J*=1.0, 8.2 Hz, 1H), 7.63 (m, 5H), 7.44 (ddd, *J*=1.3, 7.0, 8.3 Hz, 1H), 7.30 (ddd, *J*=1.3, 7.0, 8.3 Hz, 1H), 6.50 (s, 2H), 5.71 (s, 2H), 3.07 (q, *J*=7.5 Hz, 2H), 1.41 (t, *J*=7.5 Hz, 3H); MS (APCI) *m/z* 395 (*M* + *H*)⁺; Anal. calcd for C₂₂H₁₇F₃N₄: C, 67.00; H, 4.34; N, 14.21. Found: C, 66.74; H, 4.00; N, 14.19.

20

Example 9

2-Ethyl-1-[3-(2-trifluoromethylphenyl)-2-propynyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

- 25 Tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (64.5 mg, 0.03 eq.), 2-iodobenzotrifluoride (321 μL, 1.1 eq.), triethylamine (869 μL, 3.0 eq.), and copper (I) iodide (23.7 mg, 0.06 eq.) were added sequentially to a solution of 2-ethyl-1-(2-propynyl)-1*H*-imidazo[4,5-*c*]quinoline (489 mg, 2.08 mmol, 1.0 eq.) in DMF (10.6 mL). The

reaction mixture was stirred at ambient temperature for 18 hours and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel eluting with 3/97 methanol/chloroform) to provide 0.13 g of 2-ethyl-1-[3-(2-trifluoromethylphenyl)-2-propynyl]-1*H*-imidazo[4,5-*c*]quinoline as a light yellow solid.

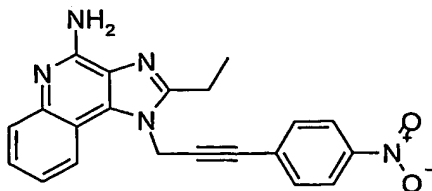
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Part B

3-Chloroperoxybenzoic acid (93 mg of 77%, 1.1 eq.) was added in a single portion to a solution of the material from Part A in chloroform (3.4 mL). The reaction mixture was stirred at ambient temperature for 45 minutes at which time analysis by TLC indicated that the oxidation was complete. Ammonium hydroxide (3 mL) was added followed by tosyl chloride (75 mg, 1.15 eq). The reaction mixture was stirred vigorously for 1 hour and then diluted with chloroform (3 mL) and water (3 mL). The layers were separated and the aqueous layer was back extracted with chloroform (2 x 10 mL). The combined organics were dried over magnesium sulfate and then concentrated under reduced pressure to provide 0.14 g of a tan solid. This material was triturated with hot ethyl acetate (~12 mL), cooled to ambient temperature, isolated by filtration and rinsed with ethyl acetate (2 x 2 mL) to provide 56 mg of a light tan solid. This material was recrystallized from 1,2-dichloroethane and then dried under vacuum at 80 °C to provide 29 mg of 2-ethyl-1-[3-(2-trifluoromethylphenyl)-2-propynyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine as colorless crystals, mp 234-235°C (dec.). ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.28 (d, *J*=7.4 Hz, 1H), 7.73 (d, *J*=7.7 Hz, 1H), 7.60 (m, 4H), 7.43 (ddd, *J*=1.3, 7.0, 8.3 Hz, 1H), 7.25 (ddd, *J*=1.3, 7.0, 8.2 Hz, 1H), 6.49 (s, 2H), 5.74 (s, 2H), 3.06 (q, *J*=7.5 Hz, 2H), 1.40 (t, *J*=7.5 Hz, 3H); MS (APCI) *m/z* 395 (M + H)⁺; Anal. calcd for C₂₂H₁₇F₃N₄•0.05C₂H₄Cl₂: C, 66.47; H, 4.34; N, 14.03. Found: C, 66.10; H, 4.44; N, 13.89.

25

Example 10

2-Ethyl-1-[3-(4-nitrophenyl)-2-propynyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine

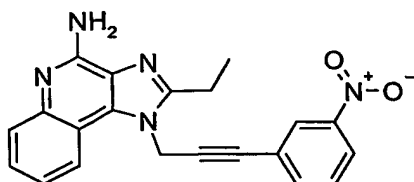
Part A

Tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (95 mg, 0.03 eq.), 4-iodonitrobenzene (0.84 g, 1.1 eq.), triethylamine (0.92 g, 3 eq.), and copper (I) iodide (35 mg, 0.06 eq.) were added sequentially to a solution of 2-ethyl-1-(2-propynyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.72 g, 3.0 mmol, 1.0 eq.) in DMF. The reaction mixture was stirred at ambient temperature overnight. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane (30 mL) and water (50 mL). The organic layer was separated, washed twice with water, and then concentrated under reduced pressure to a solid. This material was purified by column chromatography (silica gel eluting with 3/97 methanol/dichloromethane) to provide 0.4 g of 2-ethyl-1-[3-(4-nitrophenyl)-2-propynyl]-1*H*-imidazo[4,5-*c*]quinoline.

Part B

3-Chloroperoxybenzoic acid (0.365 g of 70%, 1.1 eq) was added in portions to a solution of the material from Part A in dichloromethane. When analysis by TLC indicated that the oxidation was complete, excess concentrated ammonium hydroxide was added and the reaction mixture was stirred vigorously. Tosyl chloride (0.262 mg, 1.1 eq.) was added in portions and the reaction mixture was stirred at ambient temperature for 1 hour. The organic layer was separated, washed sequentially with 5% sodium carbonate (2 x 50 mL) and water (50 mL), and concentrated under reduced pressure to provide 0.6 g of crude product as an oil. This oil was purified by column chromatography (silica gel eluting sequentially with dichloromethane and 2/98 methanol/dichloromethane) followed by recrystallization from dichloromethane to provide 16 mg of 2-ethyl-1-[3-(4-nitrophenyl)-2-propynyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a yellow granular solid, mp 190-206°C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.30 (dd, *J*=8.1, 1.1 Hz, 1H), 8.17 (d, *J*=8.9 Hz, 2H), 7.62 (m, 3H), 7.44 (ddd, *J*=1.4, 7.0, 8.3 Hz, 1H), 7.29 (ddd, *J*=1.4, 7.0, 8.3 Hz, 1H), 6.51 (s, 2H), 5.77 (s, 2H), 3.07 (q, *J*=7.4 Hz, 2H), 1.40 (t, *J*=7.4 Hz, 3H); MS (APCI) *m/z* 372 (*M* + *H*)⁺; Anal. calcd for C₂₁H₁₇N₅O₂•0.5H₂O: C, 66.31; H, 4.77; N, 18.41. Found: C, 66.13; H, 4.61; N, 18.21.

Example 11

2-Ethyl-1-[3-(3-nitrophenyl)-2-propynyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine

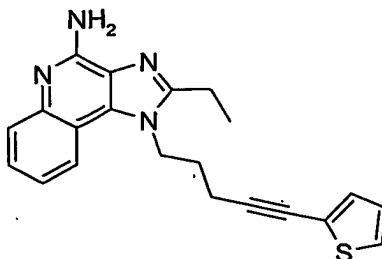
5 Part A

Tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (0.395 mg, 0.03 eq.), 3-iodonitrobenzene (3.5 g, 1.1 eq.), triethylamine (3.87 g, 3 eq.), and copper (I) iodide (0.145 g, 0.06 eq.) were added sequentially to a solution of 2-ethyl-1-(2-propynyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (3 g, 13 mmol, 1.0 eq.) in DMF. The reaction mixture was stirred at ambient temperature for 3.5 hours. A precipitate was isolated by filtration and then recrystallized from dichloromethane to provide 2.6 g of 2-ethyl-1-[3-(3-nitrophenyl)-2-propynyl]-1*H*-imidazo[4,5-*c*]quinoline as a solid.

Part B

3-Chloroperoxybenzoic acid (1.38 g, 1.1 eq.) was added in portions to a solution of the material from Part A in dichloromethane (25 mL). Two additional portions (0.25 eq. each) of 3-chloroperoxybenzoic acid were added at ½ hour and 1 hour. The reaction mixture was filtered to remove some black material. Concentrated ammonium hydroxide (20 mL) was added to the filtrate. Tosyl chloride (1.53 g, 1.1 eq.) was added in portions with vigorous stirring. A precipitate was isolated by filtration, recrystallized from *N*-methylpyrrolidine and dried under vacuum at 80 °C to provide 0.2 g of 2-ethyl-1-[3-(3-nitrophenyl)-2-propynyl]-1*H*-imidazo[4,5-*c*]quinoline-4-amine as yellow powder, mp 224-243 °C. ¹H NMR (300 MHz, TFA-*d*) δ 8.76 (d, *J*=8.6 Hz, 1H), 8.31 (m, 2H), 8.08 (t, *J*=8.3 Hz, 1H), 7.96 (m, 2H), 7.79 (dd, *J*=1.2, 7.8 Hz, 1H), 7.60 (t, *J*=8.1 Hz, 1H), 5.94 (s, 2H), 3.62 (q, *J*=7.4 Hz, 2H), 1.80 (t, *J*=7.4 Hz, 3H). MS (APCI) *m/z* 372 (M + H)⁺; Anal. calcd for C₂₁H₁₇N₅O₂•0.03 DMF: C, 67.35; H, 4.77; N, 18.87. Found: C, 67.33; H, 4.77; N, 18.92.

Example 12

2-Ethyl-1-[5-(thien-2-yl)-4-pentynyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine

5 Part A

Triethylamine (11.8 g, 1.1 eq.) was added to a suspension of 4-chloro-3-nitroquinoline (20 g, 48 mmol, 1.0 eq.) in dichloromethane (200 mL). A solution of 4-aminobutan-1-ol (9.6 g, 1.1 eq.) in dichloromethane (50 mL) was added dropwise. The reaction mixture was stirred for 2 hours and then concentrated under reduced pressure. The residue was triturated with water. The resulting solid was isolated by filtration, air dried, and purified by chromatography (silica gel eluting sequentially with dichloromethane and 5/95 methanol/dichloromethane) to provide 24.2 g of 4-[(3-nitroquinolin-4-yl)amino]butan-1-ol.

15 Part B

Catalyst (5% Pd/C) was added to a suspension of 4-[(3-nitroquinolin-4-yl)amino]butan-1-ol (18.2 g, 69.6 mmol) in toluene (450 mL) in a Parr vessel. The vessel was placed on a shaker and pressurized with hydrogen. The next day ethanol (60 mL) and additional catalyst were added and the vessel was again pressurized with hydrogen. After 1 hour analysis by TLC indicated that all of the starting material had been consumed. The reaction mixture was filtered through a layer of CELITE filter aid and then concentrated under reduced pressure to provide 17 g of 4-[(3-aminoquinolin-4-yl)amino]butan-1-ol.

Part C

25 Triethyl orthopropionate (15.1 mL of 97%, 1.1 eq.) and a catalytic amount of pyridine hydrochloride were added to a solution of 4-[(3-aminoquinolin-4-yl)amino]butan-1-ol (16 g, 69 mmol, 1 eq.) in pyridine (150 mL). The reaction mixture was refluxed for 1 hour at which time analysis by TLC indicated that all of the starting material had been

consumed. The reaction mixture was concentrated under reduced pressure and the residue was triturated with water (300 mL). The resulting solid was isolated by filtration and then recrystallized from ethyl acetate to provide 8.2 g of 4-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butan-1-ol. A second crop (1.9 g) was obtained by reducing the volume of the mother liquor.

Part D

Under a nitrogen atmosphere, dimethylsulfoxide (3.6 mL, 1.5 eq.) and oxalyl chloride (3.5 mL, 1.1 eq.) were sequentially added dropwise to chilled (dry ice/acetone bath) dichloromethane (100 mL). A solution of 4-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butan-1-ol (10 g, 37 mmol, 1 eq.) in dichloromethane was added dropwise. Triethylamine (15.5 mL, 3 eq.) was added. The ice bath was removed and the reaction mixture was allowed to warm to ambient temperature. After about 2 hours analysis by TLC indicated that the reaction was complete. The reaction mixture was diluted with dichloromethane (175 mL) and water (200 mL) and made basic (pH 10) with aqueous 5% sodium carbonate. The organic layer was washed sequentially with water (2 x 200 mL) and brine (150 mL) and then concentrated under reduced pressure to provide 9.9 g of 4-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butanal.

Part E

Diethyl 1-diazo-2-oxopropylphosphonate (9.6 g, 1.2 eq.) was added to a solution of 4-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butanal (11.15 g, 41.7 mmol, 1 eq.) and potassium carbonate (11.6 g, 2 eq.) in methanol. The reaction mixture was stirred until analysis by TLC indicated that all of the starting material had been consumed. The reaction mixture was filtered and the filter cake was rinsed until clear. The filtrate was concentrated under reduced pressure to provide crude product as an oil. The oil was partitioned between dichloromethane (200 mL) and water (100 mL). The organic layer was washed sequentially with water and brine (2 x 100 mL) and then concentrated under reduced pressure to provide 8.8 g of 2-ethyl-1-(4-pentynyl)-1*H*-imidazo[4,5-*c*]quinoline.

Part F

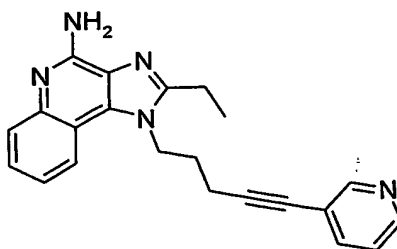
3-Chloroperoxybenzoic acid (8.0 g of 65%, 1.1 eq.) was added in portions to a solution of 2-ethyl-1-(4-pentynyl)-1*H*-imidazo[4,5-*c*]quinoline (7.2 g, 27 mmol, 1 eq.) in dichloromethane (70 mL). After 1 hour analysis by TLC indicated that the starting material had been consumed. The reaction mixture was washed sequentially with aqueous 5% sodium carbonate (3 x 100 mL), water (100 mL) and ammonium hydroxide. The organic layer was combined with 15 M ammonium hydroxide (60 mL). Tosyl chloride (5.74 g, 1.1 eq.) was added in portions with vigorous stirring. After ½ hour analysis by TLC indicated that the reaction was complete. The reaction mixture was filtered to remove a precipitate. The filtrate was diluted with dichloromethane ((100 mL). The organic layer was washed with 10% sodium hydroxide and concentrated under reduced pressure. The residue was recrystallized from a mixture of aqueous ethanol, a few drops of 10% sodium hydroxide and 1,2-dichloroethane to provide 2-ethyl-1-(4-pentynyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as beige plates, mp 219.0-223.0°C. ¹H NMR (300 MHz, CDCl₃) δ 8.01 (dd, J = 8.2, 0.9 Hz, 1H), 7.79 (dd, J = 8.4, 0.9 Hz, 1H), 7.50 (ddd, J = 8.4, 7.0, 1.4 Hz, 1H), 7.30 (dt, J = 8.3, 7.0, 1.4 Hz, 1H), 4.58 (t, J = 7.9 Hz, 2H), 2.98 (q, J = 7.4 Hz, 2H), 2.39 (m, 2H), 2.15 (m, 3H), 1.49 (t, J = 7.4 Hz, 3H); MS (APCI) *m/z* 279 (M + H)⁺; Anal. calcd for C₁₇H₁₈N₄•0.07 C₂H₆O: C, 73.11; H, 6.59; N, 19.90. Found: C, 73.10; H, 6.68; N, 19.91.

Part G

Tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (0.112 g, 0.03 eq.), 2-iodothiophene (3.9 g, 1.1 eq.), triethylamine (1.1 g, 3 eq.), and copper (I) iodide (0.042 g, 0.06 eq.) were added sequentially to a solution of 2-ethyl-1-(4-pentynyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1.0 g, 3.5 mmol, 1.0 eq.) in dichloromethane (20 mL). The reaction mixture was stirred at ambient temperature for 6 hours at which time analysis by liquid chromatography/mass spectroscopy indicated that the reaction was complete. The reaction mixture was absorbed onto the top of a column of silica gel (30 g) and the column was eluted sequentially with dichloromethane and 3/97 methanol/dichloromethane. The product was recrystallized from 1,2-dichloroethane to provide 0.25 g of 2-ethyl-1-[5-(thien-2-yl)-4-pentynyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine as an off white powder, mp 175.0-190.0 °C (dec.). ¹H NMR (300 MHz, CDCl₃) δ

8.09 (dd, $J = 8.3, 1.0$ Hz, 1H), 7.82 (dd, $J = 8.3, 1.0$ Hz, 1H), 7.48 (ddd, $J = 8.4, 6.9, 1.3$ Hz, 1H), 7.24 (m, 3H), 6.99 (dd, $J = 5.1, 3.6$ Hz, 1H), 5.37 (s, 2H), 4.65 (t, $J = 7.7$ Hz, 2H), 3.01 (q, $J = 7.5$ Hz, 2H), 2.63 (t, $J = 6.2$ Hz, 2H), 2.23 (m, 2H), 1.49 (t, $J = 7.4$ Hz, 3H); MS (APCI) m/z 361 ($M + H$)⁺; Anal. calcd for $C_{21}H_{20}N_4S \cdot 0.03 C_2H_4Cl_2$: C, 69.88; H, 5.59; N, 15.51. Found: C, 69.59; H, 5.69; N, 15.34.

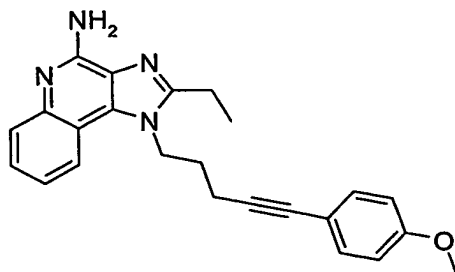
Example 13

2-Ethyl-1-[5-(pyridin-2-yl)-4-pentynyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine

Tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (0.095 g, 0.03 eq.), 3-iodopyridine (0.626 g, 1.1 eq.), triethylamine (0.923 g, 3 eq.), and copper (I) iodide (0.035 g, 0.06 eq.) were added sequentially to a solution of 2-ethyl-1-(4-pentynyl) 1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.85 g, 3.0 mmol, 1.0 eq.) in DMF. The reaction mixture was stirred for 1 hour and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel eluting with 4/96 methanol/dichloromethane). The product was recrystallized from a mixture of ethanol and 1,2-dichloroethane. The resulting solid was dissolved in 1:1 mixture of ethanol and 1,2-dichloroethane, treated with activated charcoal, combined with a few drops of 10% sodium hydroxide, heated and then filtered while still hot. The filtrate was concentrated under reduced pressure to provide 0.2 g of 2-ethyl-1-[5-(pyridin-2-yl)-4-pentynyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine as light brown granules, mp 188.0-192.0°C. ¹H NMR (300 MHz, CDCl₃) δ 8.70 (d, $J = 0.9$ Hz, 1H), 8.55 (dd, $J = 4.7, 1.3$ Hz, 1H), 8.06 (dd, $J = 8.2, 0.9$ Hz, 1H), 7.82 (dd, $J = 8.4, 0.7$ Hz, 1H), 7.71 (ddd, $J = 7.9, 1.7, 1.7$ Hz, 1H), 7.48 (ddd, $J = 8.3, 7.2, 1.2$ Hz, 1H), 7.25 (m, 2H), 5.46 (br s, 2H), 4.66 (t, $J = 7.9$ Hz, 2H), 3.00 (q, $J = 7.4$ Hz, 2H), 2.64 (t, $J = 6.5$ Hz, 2H), 2.26 (m, 2H), 1.49 (t, $J = 7.4$ Hz, 3H); MS

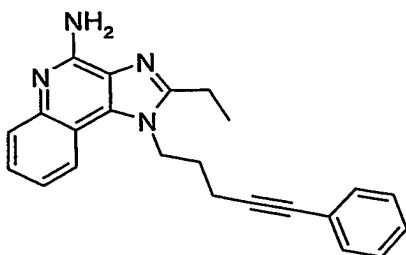
(APCI) m/z 356 ($M + H$)⁺; Anal. calcd for $C_{22}H_{21}N_5 \cdot 0.65 H_2O$: C, 71.97; H, 6.12; N, 19.07. Found: C, 72.03; H, 6.06; N, 19.16.

Example 14

2-Ethyl-1-[5-(4-methoxyphenyl)-4-pentynyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine

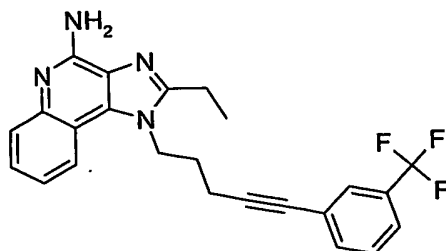
Tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (0.095 g, 0.03 eq.), 4-iodoanisole (0.786 g, 1.1 eq.), triethylamine (1.3 mL, 3 eq.), and copper (I) iodide (0.035 g, 0.06 eq.) were added sequentially to a solution of 2-ethyl-1-(4-pentynyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.85 g, 3.0 mmol, 1.0 eq.) in DMF. The reaction mixture was stirred for about 4 hours and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel eluting with 4/96 methanol/dichloromethane) to provide an oil. The oil was recrystallized from ethanol to provide 2-ethyl-1-[5-(4-methoxyphenyl)-4-pentynyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine hydroiodide as off white granules, mp 230.0°C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.14 (broad s, 1H), 8.65 (broad s, 2H), 8.37 (d, J = 8.6 Hz, 1H), 7.83 (dd, J = 8.4, 0.8 Hz, 1H), 7.68 (t, J = 7.4 Hz, 1H), 7.41 (dt, J = 8.1, 0.7 Hz, 1H), 7.34 (m, 2H), 6.93 (m, 2H), 4.73 (t, J = 7.5 Hz, 2H), 3.77 (s, 3H), 3.08 (q, J = 7.4 Hz, 2H), 2.66 (t, J = 6.9 Hz, 2H), 2.09 (m, 2H), 1.41 (t, J = 7.4 Hz, 3H); MS (APCI) m/z 385 ($M + H$)⁺; Anal. calcd for $C_{24}H_{24}N_4O_1 \cdot HI \cdot 0.08 C_2H_4Cl_2$: C, 55.30; H, 4.89; N, 10.69. Found: C, 55.39; H, 4.88; N, 10.63.

Example 15

2-Ethyl-1-(5-phenyl-4-pentynyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine

5 Tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (0.095 g, 0.03 eq.), iodobenzene (0.685 g, 1.1 eq.), triethylamine (0.923 g, 3 eq.), and copper (I) iodide (0.035 g, 0.06 eq.) were added sequentially to a solution of 2-ethyl-1-(4-pentynyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.85 g, 3.0 mmol, 1.0 eq.) in DMF. The reaction mixture was stirred for 1 hour and then concentrated under reduced pressure. The residue was
10 purified by column chromatography (silica gel eluting with 4/96 methanol/dichloromethane) to provide an oil. The oil was recrystallized from a mixture of ethanol and 1,2-dichloroethane. The resulting solid was dissolved in 1:1 mixture of ethanol and 1,2-dichloroethane, treated with activated charcoal, combined with a few drops of 10% sodium hydroxide, heated, and then filtered while still hot. The filtrate was
15 concentrated under reduced pressure to provide 0.28 g of 2-ethyl-1-(5-phenyl-4-pentynyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as white granules, mp 199.0-202.0°C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.18 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.60 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.35-7.48 (m, 6H), 7.09 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 6.46 (s, 2H), 4.61 (t, *J* = 7.8 Hz, 2H), 3.01 (q, *J* = 7.4 Hz, 2H), 2.66 (t, *J* = 6.5 Hz, 2H), 2.09 (m, 2H), 1.38 (t, *J* = 7.4 Hz, 3H); MS
20 (APCI) *m/z* 355 (*M* + *H*)⁺; Anal. calcd for C₂₃H₂₂N₄•0.02 C₂H₄Cl₂: C, 77.64; H, 6.24; N, 15.72. Found: C, 77.68; H, 6.19; N, 15.64.

Example 16

2-Ethyl-1-[5-(3-trifluoromethylphenyl)-4-pentynyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine

5 Tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (0.095 g, 0.03 eq.), 3-iodobenzotrifluoride (0.91 g, 1.1 eq.), triethylamine (0.923 g, 3 eq.), and copper (I) iodide (0.035 g, 0.06 eq.) were added sequentially to a solution of 2-ethyl-1-(4-pentynyl) 1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.85 g, 3.0 mmol, 1.0 eq.) in DMF. The reaction mixture was stirred for 1.5 hours and then concentrated under reduced pressure. The residue was partitioned between dichloromethane (50 mL) and water (50 mL). The organic layer was washed sequentially with water (3 x 30 mL) and brine and then concentrated under reduced pressure. H NMR of the residue showed the presence of DMF so the partitioning, washing and concentrating procedure was repeated to provide 0.7 g of a bright yellow solid. This solid was triturated with hot methanol to provide a white solid.

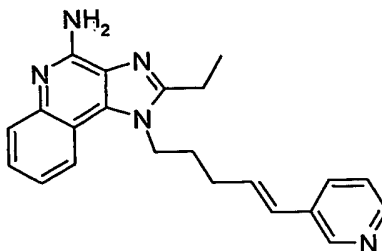
10 This solid was recrystallized from aqueous ethanol containing several drops of 10% sodium hydroxide to provide 2-ethyl-1-[5-(3-trifluoromethylphenyl)-4-pentynyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine as off white granules, mp 178.0-181.0 °C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.19 (d, *J* = 8.4 Hz, 1H), 7.79 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.63 (t, *J* = 7.9 Hz, 2H), 7.38 (broad s, 1H), 7.08 (m, 1H), 6.45 (broad s, 2H), 4.68 (t, *J* = 7.8 Hz, 2H), 3.01 (q, *J* = 7.4 Hz, 2H), 2.70 (t, *J* = 6.7 Hz, 2H), 2.10 (m, 2H), 1.38 (t, *J* = 7.4 Hz, 3H); MS (APCI) *m/z* 423 (*M* + *H*)⁺; Anal. calcd for C₂₄H₂₁F₃N₄•0.27 H₂O: C, 67.46; H, 5.08; N, 13.11. Found: C, 67.34; H, 4.75; N, 13.11.

15

20

Example 17

(E)-2-Ethyl-1-[5-(pyridin-3-yl)-4-pentenyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine



5 Part A

Bis(cyclopentadienyl)zirconium chloride hydride (20.57 g, 2.2 eq.) was added in two portions to a stirred solution of 2-ethyl-1-(4-pentynyl)-1*H*-imidazo[4,5-*c*]quinoline (9.55 g, 36.3 mmol, 1.0 eq.) in dichloromethane (180 mL). The reaction mixture was cooled for several minutes in an ice bath. After 45 minutes analysis by high performance liquid chromatography (HPLC) indicated that the reaction was complete. Solid iodine (11.04 g, 1.2 eq.) was added in a single portion. The reaction mixture was stirred for 1 hour and then combined with water (100 mL) and sodium sulfate (1 g). The reaction mixture was stirred for several minutes and then poured into a mixture of water (400 mL) and chloroform (200 mL). The mixture was made basic (pH ~8-9) with 10% sodium hydroxide. The organic layer was separated and the aqueous layer was extracted with chloroform (2 x 200 mL). The combined organics were dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and then concentrated under reduced pressure to provide 15.6 g of brown foam. This material was purified on a HORIZON High-Performance Flash Chromatography instrument (available from Biotage, Inc, Charlottesville, Virginia, USA) (silica gel eluting with a gradient of 4/96 to 11/89 methanol/chloroform) to provide 10.5 g of brown solid. This material was triturated with acetonitrile (~75 mL), isolated by filtration, rinsed with acetonitrile (2 x 20 mL) and dried under vacuum to provide 7.21 g of (E)-2-ethyl-1-(5-iodo-4-pentenyl)-1*H*-imidazo[4,5-*c*]quinoline as a tan solid.

25 Part B

3-Chloroperoxy benzoic acid (5.44 g of 77%, 1.2 eq.) was added to a solution of the material from Part A in chloroform (180 mL). After 45 minutes additional 3-chloroperoxybenzoic acid (0.15 eq.) was added and the reaction mixture was stirred for 1

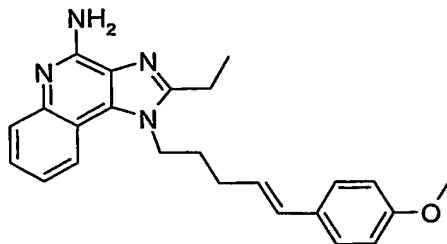
hour. Ammonium hydroxide (60 mL) and tosyl chloride (4.38 g, 1.25 eq.) were added in a single portion and the reaction mixture was stirred for 3 hours. The layers were separated and the aqueous layer was extracted with chloroform (1 x 50 mL). The combined organics were dried over magnesium sulfate and then concentrated under reduced pressure to provide 10.07 g of brown solid. This material was triturated with acetonitrile (~50 mL), isolated by filtration, rinsed with acetonitrile (2 x 20 mL) and dried under vacuum to provide 5.56 g of (E)-2-ethyl-1-(5-iodo-4-pentenyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a tan solid.

Part C

Water (4 mL), 3-pyridineboronic acid, 1,3-propanediol cyclic ester (450 mg, 1.4 eq.), triphenylphosphine (31 mg, 0.06 eq.), palladium (II) acetate (9 mg, 0.02 eq.), and 2 M aqueous sodium carbonate (2.95 mL, 3.0 eq.) were added to a stirred suspension of (E)-2-ethyl-1-(5-iodo-4-pentenyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (800 mg, 1.97 mmol, 1.0 eq.) in ethanol (16 mL). The resulting suspension was heated at 70 °C under nitrogen for 21 hours. Additional palladium (II) acetate (0.01 eq.) was added and the reaction mixture was heated for an additional 3 hours. The reaction mixture was cooled to ambient temperature and the bulk of the ethanol was removed under reduced pressure. The residue was partitioned between dichloromethane (150 mL) and water (150 mL). The aqueous layer was back extracted with dichloromethane (2 x 50 mL). The combined organics were dried over magnesium sulfate and then concentrated under reduced pressure to provide 0.66 of tan foam. This material was purified on a HORIZON High-Performance Flash Chromatography instrument (silica gel eluting with 0-20% 80/18/2 chloroform/methanol/ammonium hydroxide (CMA) in dichloromethane for 672 mL and 20-30% CMA in dichloromethane for 192 mL to provide 212 mg of a white solid which was dried at 60 °C for 16 hours to provide (E)-2-ethyl-1-[5-(pyridin-3-yl)-4-pentenyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white powder, mp 188-190°C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.59 (d, *J*=1.6 Hz, 1H), 8.40 (dd, *J*=1.6, 4.8 Hz, 1H), 8.04 (d, *J*=7.6 Hz, 1H), 7.84 (ddd, *J*=1.9, 1.9, 7.8 Hz, 1H), 7.60 (dd, *J*=1.2, 7.2, 8.3 Hz, 1H), 7.40 (ddd, *J*=1.2, 7.2, 8.3 Hz, 1H), 7.33 (dd, *J*=4.8, 8.1 Hz, 1H), 7.17 (ddd, *J*=1.2, 7.2, 8.3 Hz, 1H), 6.47 (m, 4H), 4.57 (t, *J*=7.5 Hz, 2H), 2.97 (q, *J*=7.5 Hz, 2H), 2.39 (m, 2H), 2.01 (m, 2H), 1.38 (t, *J*=7.5 Hz, 3H); MS (APCI) *m/z* 358 (M + H)⁺; Anal. calcd for C₂₂H₂₃N₅: C, 73.92; H, 6.49; N, 19.59. Found: C, 73.60; H, 6.27; N, 19.37.

Example 18

(E)-2-Ethyl-1-[5-(4-methoxyphenyl)-4-pentenyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine



5 Water (0.1 mL), 4-methoxyphenylboronic acid (449 mg, 1.2 eq.), triphenylphosphine (39 mg, 0.06 eq.), palladium (II) acetate (11 mg, 0.02 eq.), and 2 M aqueous sodium carbonate (3.7 mL, 3.0 eq.) were added to a stirred suspension of (E)-2-ethyl-1-(5-iodo-4-pentenyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1.00 g mg, 2.46 mmol, 1.0 eq.) in ethanol (0.5 mL). The resulting suspension was heated at 70 °C under nitrogen for 4.5 hours. Additional triphenylphosphine (0.05 eq.), palladium (II) acetate (0.02 eq.) and 4-methoxyphenylboronic acid (0.3 eq.) were added and the reaction mixture was stirred for another 5 hours. The reaction mixture was cooled to ambient temperature and the bulk of the ethanol was removed under reduced pressure. The residue was partitioned between dichloromethane (100 mL) and water (50 mL). The aqueous layer was back extracted with dichloromethane (1 x 50 mL). The combined organics were dried over magnesium sulfate and then concentrated under reduced pressure to provide 1.11 g of brown foam. This material was purified on a HORIZON High-Performance Flash Chromatography instrument (silica gel eluting with 0-10 % CMA in dichloromethane over 480 mL, 10% CMA in dichloromethane over 380 mL, 10-20% CMA in dichloromethane over 192 mL, 20-30% CMA in dichloromethane over 192 mL, and 30% CMA in dichloromethane for 210 mL) to provide 0.44 g of white solid. This material was recrystallized from ethanol (~10 mL) to provide 294 mg of (E)-2-ethyl-1-[5-(4-methoxyphenyl)-4-pentenyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white powder, mp 179-180°C. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.04 (d, J=8.0 Hz, 1H), 7.60 (d, J=8.4 Hz, 1H), 7.40 (m, 1H), 7.34 (d, J=8.6 Hz, 2H), 7.17 (t, J=8.6 Hz, 1H), 6.88 (d, J=8.6 Hz, 2H), 6.44 (br s, 2H), 6.40 (d, J=15.8 Hz, 1H), 6.19 (ddd, J=6.4, 6.4, 15.8 Hz, 1H), 4.54 (t, J=7.6 Hz, 2H), 3.74 (s, 3H), 2.96 (q, J=7.6 Hz, 2H), 2.34 (m, 2H), 1.98 (m, 2H), 1.37 (t, J=7.5

Hz, 3H); MS (APCI) m/z 387 ($M + H$)⁺; Anal. calcd. for C₂₄H₂₆N₄O: C, 74.58; H, 6.78; N, 14.50. Found: C, 74.25; H, 6.61; N, 14.35.

CYTOKINE INDUCTION IN HUMAN CELLS

5 The compounds of Examples 1 - 18 have been found to modulate cytokine biosynthesis by inducing the production of interferon α and/or tumor necrosis factor α when tested using the method described below.

10 An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon and tumor necrosis factor (α) (IFN and TNF, respectively) secreted into culture media as described by Testerman et. al. in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", *Journal of Leukocyte Biology*, 58, 365-372 (September, 1995).

15 Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into EDTA vacutainer tubes. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077. Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). The PBMC layer is collected and washed twice with DPBS or HBSS and resuspended at 4×10^6 cells/mL in RPMI complete. The PBMC suspension is added to 48 well flat bottom sterile tissue culture plates (Costar, Cambridge, MA or Becton Dickinson Labware, Lincoln Park, NJ) containing an equal volume of RPMI complete media containing test compound.

25 Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μ M.

30 Incubation

The solution of test compound is added at 60 μ M to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (30-0.014 μ M). The final concentration of PBMC suspension is 2×10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed with a sterile polypropylene pipet and transferred to sterile polypropylene tubes. Samples are maintained at -30 to -70°C until analysis. The samples are analyzed for interferon (α) by ELISA and for tumor necrosis factor (α) by ELISA or IGEN Assay

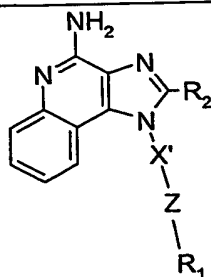
Interferon (α) and Tumor Necrosis Factor (α) Analysis by ELISA

Interferon (α) concentration is determined by ELISA using a Human Multi-Species kit from PBL Biomedical Laboratories, New Brunswick, NJ. Results are expressed in pg/mL.

Tumor necrosis factor (α) (TNF) concentration is determined using ELISA kits available from Biosource International, Camarillo, CA. Alternately, the TNF concentration can be determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF capture and detection antibody pair from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

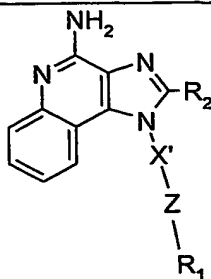
Exemplary Compounds

Certain exemplary compounds have the Formula (IIa) and the following substituents, wherein each line of the table represents a specific compound. These compounds may be prepared using the synthetic methods described above.



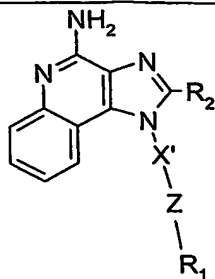
IIa

X'	Z	R ₁	R ₂
-CH ₂ -	-C≡C-	phenyl	methyl
-CH ₂ -	-C≡C-	phenyl	propyl
-CH ₂ -	-C≡C-	phenyl	butyl
-CH ₂ -	-C≡C-	phenyl	ethoxymethyl
-CH ₂ -	-C≡C-	phenyl	2-methoxyethyl
-CH ₂ -	-C≡C-	4-chlorophenyl	methyl
-CH ₂ -	-C≡C-	4-chlorophenyl	ethyl
-CH ₂ -	-C≡C-	4-chlorophenyl	propyl
-CH ₂ -	-C≡C-	4-chlorophenyl	butyl
-CH ₂ -	-C≡C-	4-chlorophenyl	ethoxymethyl
-CH ₂ -	-C≡C-	4-chlorophenyl	2-methoxyethyl
-CH ₂ -	-C≡C-	3-chlorophenyl	methyl
-CH ₂ -	-C≡C-	3-chlorophenyl	ethyl
-CH ₂ -	-C≡C-	3-chlorophenyl	propyl
-CH ₂ -	-C≡C-	3-chlorophenyl	butyl
-CH ₂ -	-C≡C-	3-chlorophenyl	ethoxymethyl
-CH ₂ -	-C≡C-	3-chlorophenyl	2-methoxyethyl
-CH ₂ -	-C≡C-	4-fluorophenyl	methyl
-CH ₂ -	-C≡C-	4-fluorophenyl	ethyl
-CH ₂ -	-C≡C-	4-fluorophenyl	propyl
-CH ₂ -	-C≡C-	4-fluorophenyl	butyl
-CH ₂ -	-C≡C-	4-fluorophenyl	ethoxymethyl
-CH ₂ -	-C≡C-	4-fluorophenyl	2-methoxyethyl



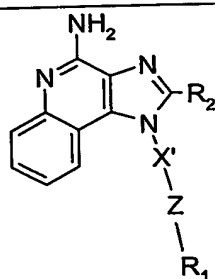
IIa

X'	Z	R ₁	R ₂
-CH ₂ -	-C≡C-	3-fluorophenyl	methyl
-CH ₂ -	-C≡C-	3-fluorophenyl	ethyl
-CH ₂ -	-C≡C-	3-fluorophenyl	propyl
-CH ₂ -	-C≡C-	3-fluorophenyl	butyl
-CH ₂ -	-C≡C-	3-fluorophenyl	ethoxymethyl
-CH ₂ -	-C≡C-	3-fluorophenyl	2-methoxyethyl
-CH ₂ -	-C≡C-	4-methoxyphenyl	methyl
-CH ₂ -	-C≡C-	4-methoxyphenyl	propyl
-CH ₂ -	-C≡C-	4-methoxyphenyl	butyl
-CH ₂ -	-C≡C-	4-methoxyphenyl	ethoxymethyl
-CH ₂ -	-C≡C-	4-methoxyphenyl	2-methoxyethyl
-CH ₂ -	-C≡C-	3-methoxyphenyl	methyl
-CH ₂ -	-C≡C-	3-methoxyphenyl	ethyl
-CH ₂ -	-C≡C-	3-methoxyphenyl	propyl
-CH ₂ -	-C≡C-	3-methoxyphenyl	butyl
-CH ₂ -	-C≡C-	3-methoxyphenyl	ethoxymethyl
-CH ₂ -	-C≡C-	3-methoxyphenyl	2-methoxyethyl
-CH ₂ -	-C≡C-	4-trifluoromethylphenyl	methyl
-CH ₂ -	-C≡C-	4-trifluoromethylphenyl	ethyl
-CH ₂ -	-C≡C-	4-trifluoromethylphenyl	propyl
-CH ₂ -	-C≡C-	4-trifluoromethylphenyl	butyl
-CH ₂ -	-C≡C-	4-trifluoromethylphenyl	ethoxymethyl
-CH ₂ -	-C≡C-	4-trifluoromethylphenyl	2-methoxyethyl



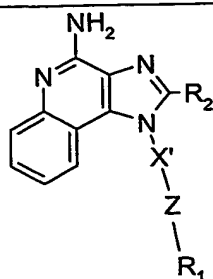
IIa

X'	Z	R ₁	R ₂
-CH ₂ -	-C≡C-	3-trifluoromethylphenyl	methyl
-CH ₂ -	-C≡C-	3-trifluoromethylphenyl	propyl
-CH ₂ -	-C≡C-	3-trifluoromethylphenyl	butyl
-CH ₂ -	-C≡C-	3-trifluoromethylphenyl	ethoxymethyl
-CH ₂ -	-C≡C-	3-trifluoromethylphenyl	2-methoxyethyl
-CH ₂ -	-C≡C-	2-pyridinyl	methyl
-CH ₂ -	-C≡C-	2-pyridinyl	ethyl
-CH ₂ -	-C≡C-	2-pyridinyl	propyl
-CH ₂ -	-C≡C-	2-pyridinyl	butyl
-CH ₂ -	-C≡C-	2-pyridinyl	ethoxymethyl
-CH ₂ -	-C≡C-	2-pyridinyl	2-methoxyethyl
-CH ₂ -	-C≡C-	3-pyridinyl	methyl
-CH ₂ -	-C≡C-	3-pyridinyl	propyl
-CH ₂ -	-C≡C-	3-pyridinyl	butyl
-CH ₂ -	-C≡C-	3-pyridinyl	ethoxymethyl
-CH ₂ -	-C≡C-	3-pyridinyl	2-methoxyethyl
-CH ₂ -	-CH=CH-	phenyl	methyl
-CH ₂ -	-CH=CH-	phenyl	ethyl
-CH ₂ -	-CH=CH-	phenyl	propyl
-CH ₂ -	-CH=CH-	phenyl	butyl
-CH ₂ -	-CH=CH-	phenyl	ethoxymethyl
-CH ₂ -	-CH=CH-	phenyl	2-methoxyethyl
-CH ₂ -	-CH=CH-	4-chlorophenyl	methyl



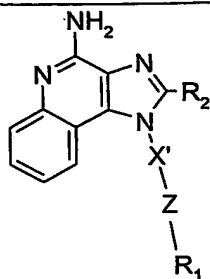
IIa

X'	Z	R ₁	R ₂
-CH ₂ -	-CH=CH-	4-chlorophenyl	ethyl
-CH ₂ -	-CH=CH-	4-chlorophenyl	propyl
-CH ₂ -	-CH=CH-	4-chlorophenyl	butyl
-CH ₂ -	-CH=CH-	4-chlorophenyl	ethoxymethyl
-CH ₂ -	-CH=CH-	4-chlorophenyl	2-methoxyethyl
-CH ₂ -	-CH=CH-	3-chlorophenyl	methyl
-CH ₂ -	-CH=CH-	3-chlorophenyl	ethyl
-CH ₂ -	-CH=CH-	3-chlorophenyl	propyl
-CH ₂ -	-CH=CH-	3-chlorophenyl	butyl
-CH ₂ -	-CH=CH-	3-chlorophenyl	ethoxymethyl
-CH ₂ -	-CH=CH-	3-chlorophenyl	2-methoxyethyl
-CH ₂ -	-CH=CH-	4-fluorophenyl	methyl
-CH ₂ -	-CH=CH-	4-fluorophenyl	ethyl
-CH ₂ -	-CH=CH-	4-fluorophenyl	propyl
-CH ₂ -	-CH=CH-	4-fluorophenyl	butyl
-CH ₂ -	-CH=CH-	4-fluorophenyl	ethoxymethyl
-CH ₂ -	-CH=CH-	4-fluorophenyl	2-methoxyethyl
-CH ₂ -	-CH=CH-	3-fluorophenyl	methyl
-CH ₂ -	-CH=CH-	3-fluorophenyl	ethyl
-CH ₂ -	-CH=CH-	3-fluorophenyl	propyl
-CH ₂ -	-CH=CH-	3-fluorophenyl	butyl
-CH ₂ -	-CH=CH-	3-fluorophenyl	ethoxymethyl
-CH ₂ -	-CH=CH-	3-fluorophenyl	2-methoxyethyl



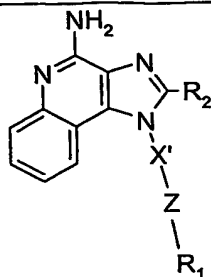
IIa

X'	Z	R ₁	R ₂
-CH ₂ -	-CH=CH-	4-methoxyphenyl	methyl
-CH ₂ -	-CH=CH-	4-methoxyphenyl	ethyl
-CH ₂ -	-CH=CH-	4-methoxyphenyl	propyl
-CH ₂ -	-CH=CH-	4-methoxyphenyl	butyl
-CH ₂ -	-CH=CH-	4-methoxyphenyl	ethoxymethyl
-CH ₂ -	-CH=CH-	4-methoxyphenyl	2-methoxyethyl
-CH ₂ -	-CH=CH-	3-methoxyphenyl	methyl
-CH ₂ -	-CH=CH-	3-methoxyphenyl	ethyl
-CH ₂ -	-CH=CH-	3-methoxyphenyl	propyl
-CH ₂ -	-CH=CH-	3-methoxyphenyl	butyl
-CH ₂ -	-CH=CH-	3-methoxyphenyl	ethoxymethyl
-CH ₂ -	-CH=CH-	3-methoxyphenyl	2-methoxyethyl
-CH ₂ -	-CH=CH-	4-trifluoromethylphenyl	methyl
-CH ₂ -	-CH=CH-	4-trifluoromethylphenyl	ethyl
-CH ₂ -	-CH=CH-	4-trifluoromethylphenyl	propyl
-CH ₂ -	-CH=CH-	4-trifluoromethylphenyl	butyl
-CH ₂ -	-CH=CH-	4-trifluoromethylphenyl	ethoxymethyl
-CH ₂ -	-CH=CH-	4-trifluoromethylphenyl	2-methoxyethyl
-CH ₂ -	-CH=CH-	3-trifluoromethylphenyl	methyl
-CH ₂ -	-CH=CH-	3-trifluoromethylphenyl	ethyl
-CH ₂ -	-CH=CH-	3-trifluoromethylphenyl	propyl
-CH ₂ -	-CH=CH-	3-trifluoromethylphenyl	butyl
-CH ₂ -	-CH=CH-	3-trifluoromethylphenyl	ethoxymethyl



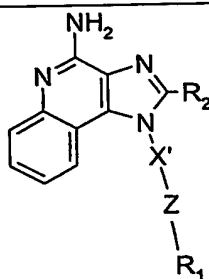
IIa

X'	Z	R ₁	R ₂
-CH ₂ -	-CH=CH-	3-trifluoromethylphenyl	2-methoxyethyl
-CH ₂ -	-CH=CH-	2-pyridinyl	methyl
-CH ₂ -	-CH=CH-	2-pyridinyl	ethyl
-CH ₂ -	-CH=CH-	2-pyridinyl	propyl
-CH ₂ -	-CH=CH-	2-pyridinyl	butyl
-CH ₂ -	-CH=CH-	2-pyridinyl	ethoxymethyl
-CH ₂ -	-CH=CH-	2-pyridinyl	2-methoxyethyl
-CH ₂ -	-CH=CH-	3-pyridinyl	methyl
-CH ₂ -	-CH=CH-	3-pyridinyl	ethyl
-CH ₂ -	-CH=CH-	3-pyridinyl	propyl
-CH ₂ -	-CH=CH-	3-pyridinyl	butyl
-CH ₂ -	-CH=CH-	3-pyridinyl	ethoxymethyl
-CH ₂ -	-CH=CH-	3-pyridinyl	2-methoxyethyl
-(CH ₂) ₂ -	-C≡C-	phenyl	methyl
-(CH ₂) ₂ -	-C≡C-	phenyl	ethyl
-(CH ₂) ₂ -	-C≡C-	phenyl	propyl
-(CH ₂) ₂ -	-C≡C-	phenyl	butyl
-(CH ₂) ₂ -	-C≡C-	phenyl	ethoxymethyl
-(CH ₂) ₂ -	-C≡C-	phenyl	2-methoxyethyl
-(CH ₂) ₂ -	-C≡C-	4-chlorophenyl	methyl
-(CH ₂) ₂ -	-C≡C-	4-chlorophenyl	ethyl
-(CH ₂) ₂ -	-C≡C-	4-chlorophenyl	propyl
-(CH ₂) ₂ -	-C≡C-	4-chlorophenyl	butyl



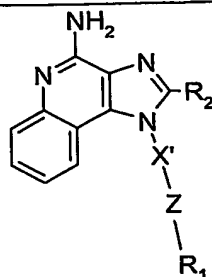
IIa

X'	Z	R ₁	R ₂
-(CH ₂) ₂ -	-C≡C-	4-chlorophenyl	ethoxymethyl
-(CH ₂) ₂ -	-C≡C-	4-chlorophenyl	2-methoxyethyl
-(CH ₂) ₂ -	-C≡C-	3-chlorophenyl	methyl
-(CH ₂) ₂ -	-C≡C-	3-chlorophenyl	ethyl
-(CH ₂) ₂ -	-C≡C-	3-chlorophenyl	propyl
-(CH ₂) ₂ -	-C≡C-	3-chlorophenyl	butyl
-(CH ₂) ₂ -	-C≡C-	3-chlorophenyl	ethoxymethyl
-(CH ₂) ₂ -	-C≡C-	3-chlorophenyl	2-methoxyethyl
-(CH ₂) ₂ -	-C≡C-	4-fluorophenyl	methyl
-(CH ₂) ₂ -	-C≡C-	4-fluorophenyl	ethyl
-(CH ₂) ₂ -	-C≡C-	4-fluorophenyl	propyl
-(CH ₂) ₂ -	-C≡C-	4-fluorophenyl	butyl
-(CH ₂) ₂ -	-C≡C-	4-fluorophenyl	ethoxymethyl
-(CH ₂) ₂ -	-C≡C-	4-fluorophenyl	2-methoxyethyl
-(CH ₂) ₂ -	-C≡C-	3-fluorophenyl	methyl
-(CH ₂) ₂ -	-C≡C-	3-fluorophenyl	ethyl
-(CH ₂) ₂ -	-C≡C-	3-fluorophenyl	propyl
-(CH ₂) ₂ -	-C≡C-	3-fluorophenyl	butyl
-(CH ₂) ₂ -	-C≡C-	3-fluorophenyl	ethoxymethyl
-(CH ₂) ₂ -	-C≡C-	3-fluorophenyl	2-methoxyethyl
-(CH ₂) ₂ -	-C≡C-	4-methoxyphenyl	methyl
-(CH ₂) ₂ -	-C≡C-	4-methoxyphenyl	ethyl
-(CH ₂) ₂ -	-C≡C-	4-methoxyphenyl	propyl



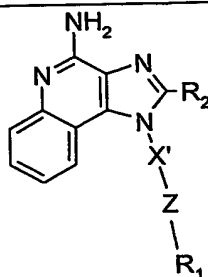
IIa

X'	Z	R ₁	R ₂
-(CH ₂) ₂ -	-C≡C-	4-methoxyphenyl	butyl
-(CH ₂) ₂ -	-C≡C-	4-methoxyphenyl	ethoxymethyl
-(CH ₂) ₂ -	-C≡C-	4-methoxyphenyl	2-methoxyethyl
-(CH ₂) ₂ -	-C≡C-	3-methoxyphenyl	methyl
-(CH ₂) ₂ -	-C≡C-	3-methoxyphenyl	ethyl
-(CH ₂) ₂ -	-C≡C-	3-methoxyphenyl	propyl
-(CH ₂) ₂ -	-C≡C-	3-methoxyphenyl	butyl
-(CH ₂) ₂ -	-C≡C-	3-methoxyphenyl	ethoxymethyl
-(CH ₂) ₂ -	-C≡C-	3-methoxyphenyl	2-methoxyethyl
-(CH ₂) ₂ -	-C≡C-	4-trifluoromethylphenyl	methyl
-(CH ₂) ₂ -	-C≡C-	4-trifluoromethylphenyl	ethyl
-(CH ₂) ₂ -	-C≡C-	4-trifluoromethylphenyl	propyl
-(CH ₂) ₂ -	-C≡C-	4-trifluoromethylphenyl	butyl
-(CH ₂) ₂ -	-C≡C-	4-trifluoromethylphenyl	ethoxymethyl
-(CH ₂) ₂ -	-C≡C-	4-trifluoromethylphenyl	2-methoxyethyl
-(CH ₂) ₂ -	-C≡C-	3-trifluoromethylphenyl	methyl
-(CH ₂) ₂ -	-C≡C-	3-trifluoromethylphenyl	ethyl
-(CH ₂) ₂ -	-C≡C-	3-trifluoromethylphenyl	propyl
-(CH ₂) ₂ -	-C≡C-	3-trifluoromethylphenyl	butyl
-(CH ₂) ₂ -	-C≡C-	3-trifluoromethylphenyl	ethoxymethyl
-(CH ₂) ₂ -	-C≡C-	3-trifluoromethylphenyl	2-methoxyethyl
-(CH ₂) ₂ -	-C≡C-	2-pyridinyl	methyl
-(CH ₂) ₂ -	-C≡C-	2-pyridinyl	ethyl



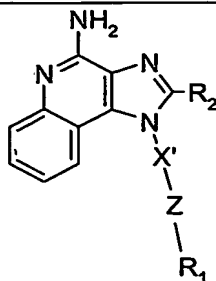
IIa

X'	Z	R ₁	R ₂
-(CH ₂) ₂ -	-C≡C-	2-pyridinyl	propyl
-(CH ₂) ₂ -	-C≡C-	2-pyridinyl	butyl
-(CH ₂) ₂ -	-C≡C-	2-pyridinyl	ethoxymethyl
-(CH ₂) ₂ -	-C≡C-	2-pyridinyl	2-methoxyethyl
-(CH ₂) ₂ -	-C≡C-	3-pyridinyl	methyl
-(CH ₂) ₂ -	-C≡C-	3-pyridinyl	ethyl
-(CH ₂) ₂ -	-C≡C-	3-pyridinyl	propyl
-(CH ₂) ₂ -	-C≡C-	3-pyridinyl	butyl
-(CH ₂) ₂ -	-C≡C-	3-pyridinyl	ethoxymethyl
-(CH ₂) ₂ -	-C≡C-	3-pyridinyl	2-methoxyethyl
-(CH ₂) ₂ -	-CH=CH-	phenyl	methyl
-(CH ₂) ₂ -	-CH=CH-	phenyl	ethyl
-(CH ₂) ₂ -	-CH=CH-	phenyl	propyl
-(CH ₂) ₂ -	-CH=CH-	phenyl	butyl
-(CH ₂) ₂ -	-CH=CH-	phenyl	ethoxymethyl
-(CH ₂) ₂ -	-CH=CH-	phenyl	2-methoxyethyl
-(CH ₂) ₂ -	-CH=CH-	4-chlorophenyl	methyl
-(CH ₂) ₂ -	-CH=CH-	4-chlorophenyl	ethyl
-(CH ₂) ₂ -	-CH=CH-	4-chlorophenyl	propyl
-(CH ₂) ₂ -	-CH=CH-	4-chlorophenyl	butyl
-(CH ₂) ₂ -	-CH=CH-	4-chlorophenyl	ethoxymethyl
-(CH ₂) ₂ -	-CH=CH-	4-chlorophenyl	2-methoxyethyl
-(CH ₂) ₂ -	-CH=CH-	3-chlorophenyl	methyl



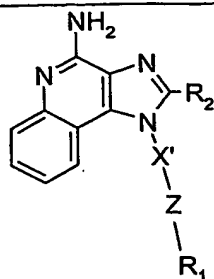
IIa

X'	Z	R ₁	R ₂
-(CH ₂) ₂ -	-CH=CH-	3-chlorophenyl	ethyl
-(CH ₂) ₂ -	-CH=CH-	3-chlorophenyl	propyl
-(CH ₂) ₂ -	-CH=CH-	3-chlorophenyl	butyl
-(CH ₂) ₂ -	-CH=CH-	3-chlorophenyl	ethoxymethyl
-(CH ₂) ₂ -	-CH=CH-	3-chlorophenyl	2-methoxyethyl
-(CH ₂) ₂ -	-CH=CH-	4-fluorophenyl	methyl
-(CH ₂) ₂ -	-CH=CH-	4-fluorophenyl	ethyl
-(CH ₂) ₂ -	-CH=CH-	4-fluorophenyl	propyl
-(CH ₂) ₂ -	-CH=CH-	4-fluorophenyl	butyl
-(CH ₂) ₂ -	-CH=CH-	4-fluorophenyl	ethoxymethyl
-(CH ₂) ₂ -	-CH=CH-	4-fluorophenyl	2-methoxyethyl
-(CH ₂) ₂ -	-CH=CH-	3-fluorophenyl	methyl
-(CH ₂) ₂ -	-CH=CH-	3-fluorophenyl	ethyl
-(CH ₂) ₂ -	-CH=CH-	3-fluorophenyl	propyl
-(CH ₂) ₂ -	-CH=CH-	3-fluorophenyl	butyl
-(CH ₂) ₂ -	-CH=CH-	3-fluorophenyl	ethoxymethyl
-(CH ₂) ₂ -	-CH=CH-	3-fluorophenyl	2-methoxyethyl
-(CH ₂) ₂ -	-CH=CH-	4-methoxyphenyl	methyl
-(CH ₂) ₂ -	-CH=CH-	4-methoxyphenyl	ethyl
-(CH ₂) ₂ -	-CH=CH-	4-methoxyphenyl	propyl
-(CH ₂) ₂ -	-CH=CH-	4-methoxyphenyl	butyl
-(CH ₂) ₂ -	-CH=CH-	4-methoxyphenyl	ethoxymethyl
-(CH ₂) ₂ -	-CH=CH-	4-methoxyphenyl	2-methoxyethyl



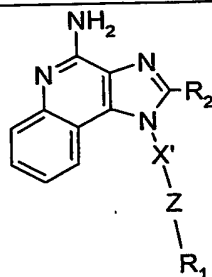
IIa

X'	Z	R ₁	R ₂
-(CH ₂) ₂ -	-CH=CH-	3-methoxyphenyl	methyl
-(CH ₂) ₂ -	-CH=CH-	3-methoxyphenyl	ethyl
-(CH ₂) ₂ -	-CH=CH-	3-methoxyphenyl	propyl
-(CH ₂) ₂ -	-CH=CH-	3-methoxyphenyl	butyl
-(CH ₂) ₂ -	-CH=CH-	3-methoxyphenyl	ethoxymethyl
-(CH ₂) ₂ -	-CH=CH-	3-methoxyphenyl	2-methoxyethyl
-(CH ₂) ₂ -	-CH=CH-	4-trifluoromethylphenyl	methyl
-(CH ₂) ₂ -	-CH=CH-	4-trifluoromethylphenyl	ethyl
-(CH ₂) ₂ -	-CH=CH-	4-trifluoromethylphenyl	propyl
-(CH ₂) ₂ -	-CH=CH-	4-trifluoromethylphenyl	butyl
-(CH ₂) ₂ -	-CH=CH-	4-trifluoromethylphenyl	ethoxymethyl
-(CH ₂) ₂ -	-CH=CH-	4-trifluoromethylphenyl	2-methoxyethyl
-(CH ₂) ₂ -	-CH=CH-	3-trifluoromethylphenyl	methyl
-(CH ₂) ₂ -	-CH=CH-	3-trifluoromethylphenyl	ethyl
-(CH ₂) ₂ -	-CH=CH-	3-trifluoromethylphenyl	propyl
-(CH ₂) ₂ -	-CH=CH-	3-trifluoromethylphenyl	butyl
-(CH ₂) ₂ -	-CH=CH-	3-trifluoromethylphenyl	ethoxymethyl
-(CH ₂) ₂ -	-CH=CH-	3-trifluoromethylphenyl	2-methoxyethyl
-(CH ₂) ₂ -	-CH=CH-	2-pyridinyl	methyl
-(CH ₂) ₂ -	-CH=CH-	2-pyridinyl	ethyl
-(CH ₂) ₂ -	-CH=CH-	2-pyridinyl	propyl
-(CH ₂) ₂ -	-CH=CH-	2-pyridinyl	butyl
-(CH ₂) ₂ -	-CH=CH-	2-pyridinyl	ethoxymethyl



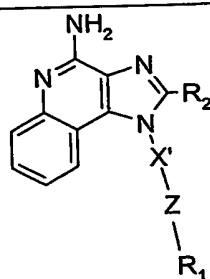
IIa

X'	Z	R ₁	R ₂
-(CH ₂) ₂ -	-CH=CH-	2-pyridinyl	2-methoxyethyl
-(CH ₂) ₂ -	-CH=CH-	3-pyridinyl	methyl
-(CH ₂) ₂ -	-CH=CH-	3-pyridinyl	ethyl
-(CH ₂) ₂ -	-CH=CH-	3-pyridinyl	propyl
-(CH ₂) ₂ -	-CH=CH-	3-pyridinyl	butyl
-(CH ₂) ₂ -	-CH=CH-	3-pyridinyl	ethoxymethyl
-(CH ₂) ₂ -	-CH=CH-	3-pyridinyl	2-methoxyethyl
-(CH ₂) ₃ -	-C≡C-	phenyl	methyl
-(CH ₂) ₃ -	-C≡C-	phenyl	propyl
-(CH ₂) ₃ -	-C≡C-	phenyl	butyl
-(CH ₂) ₃ -	-C≡C-	phenyl	ethoxymethyl
-(CH ₂) ₃ -	-C≡C-	phenyl	2-methoxyethyl
-(CH ₂) ₃ -	-C≡C-	4-chlorophenyl	methyl
-(CH ₂) ₃ -	-C≡C-	4-chlorophenyl	ethyl
-(CH ₂) ₃ -	-C≡C-	4-chlorophenyl	propyl
-(CH ₂) ₃ -	-C≡C-	4-chlorophenyl	butyl
-(CH ₂) ₃ -	-C≡C-	4-chlorophenyl	ethoxymethyl
-(CH ₂) ₃ -	-C≡C-	4-chlorophenyl	2-methoxyethyl
-(CH ₂) ₃ -	-C≡C-	3-chlorophenyl	methyl
-(CH ₂) ₃ -	-C≡C-	3-chlorophenyl	ethyl
-(CH ₂) ₃ -	-C≡C-	3-chlorophenyl	propyl
-(CH ₂) ₃ -	-C≡C-	3-chlorophenyl	butyl
-(CH ₂) ₃ -	-C≡C-	3-chlorophenyl	ethoxymethyl



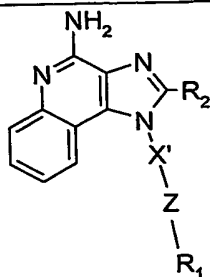
IIa

X'	Z	R ₁	R ₂
-(CH ₂) ₃ -	-C≡C-	3-chlorophenyl	2-methoxyethyl
-(CH ₂) ₃ -	-C≡C-	4-fluorophenyl	methyl
-(CH ₂) ₃ -	-C≡C-	4-fluorophenyl	ethyl
-(CH ₂) ₃ -	-C≡C-	4-fluorophenyl	propyl
-(CH ₂) ₃ -	-C≡C-	4-fluorophenyl	butyl
-(CH ₂) ₃ -	-C≡C-	4-fluorophenyl	ethoxymethyl
-(CH ₂) ₃ -	-C≡C-	4-fluorophenyl	2-methoxyethyl
-(CH ₂) ₃ -	-C≡C-	3-fluorophenyl	methyl
-(CH ₂) ₃ -	-C≡C-	3-fluorophenyl	ethyl
-(CH ₂) ₃ -	-C≡C-	3-fluorophenyl	propyl
-(CH ₂) ₃ -	-C≡C-	3-fluorophenyl	butyl
-(CH ₂) ₃ -	-C≡C-	3-fluorophenyl	ethoxymethyl
-(CH ₂) ₃ -	-C≡C-	3-fluorophenyl	2-methoxyethyl
-(CH ₂) ₃ -	-C≡C-	4-methoxyphenyl	methyl
-(CH ₂) ₃ -	-C≡C-	4-methoxyphenyl	propyl
-(CH ₂) ₃ -	-C≡C-	4-methoxyphenyl	butyl
-(CH ₂) ₃ -	-C≡C-	4-methoxyphenyl	ethoxymethyl
-(CH ₂) ₃ -	-C≡C-	4-methoxyphenyl	2-methoxyethyl
-(CH ₂) ₃ -	-C≡C-	3-methoxyphenyl	methyl
-(CH ₂) ₃ -	-C≡C-	3-methoxyphenyl	ethyl
-(CH ₂) ₃ -	-C≡C-	3-methoxyphenyl	propyl
-(CH ₂) ₃ -	-C≡C-	3-methoxyphenyl	butyl
-(CH ₂) ₃ -	-C≡C-	3-methoxyphenyl	ethoxymethyl



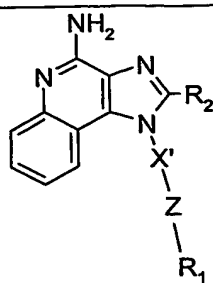
IIa

X'	Z	R ₁	R ₂
-(CH ₂) ₃ -	-C≡C-	3-methoxyphenyl	2-methoxyethyl
-(CH ₂) ₃ -	-C≡C-	4-trifluoromethylphenyl	methyl
-(CH ₂) ₃ -	-C≡C-	4-trifluoromethylphenyl	ethyl
-(CH ₂) ₃ -	-C≡C-	4-trifluoromethylphenyl	propyl
-(CH ₂) ₃ -	-C≡C-	4-trifluoromethylphenyl	butyl
-(CH ₂) ₃ -	-C≡C-	4-trifluoromethylphenyl	ethoxymethyl
-(CH ₂) ₃ -	-C≡C-	4-trifluoromethylphenyl	2-methoxyethyl
-(CH ₂) ₃ -	-C≡C-	3-trifluoromethylphenyl	methyl
-(CH ₂) ₃ -	-C≡C-	3-trifluoromethylphenyl	propyl
-(CH ₂) ₃ -	-C≡C-	3-trifluoromethylphenyl	butyl
-(CH ₂) ₃ -	-C≡C-	3-trifluoromethylphenyl	ethoxymethyl
-(CH ₂) ₃ -	-C≡C-	3-trifluoromethylphenyl	2-methoxyethyl
-(CH ₂) ₃ -	-C≡C-	2-pyridinyl	methyl
-(CH ₂) ₃ -	-C≡C-	2-pyridinyl	ethyl
-(CH ₂) ₃ -	-C≡C-	2-pyridinyl	propyl
-(CH ₂) ₃ -	-C≡C-	2-pyridinyl	butyl
-(CH ₂) ₃ -	-C≡C-	2-pyridinyl	ethoxymethyl
-(CH ₂) ₃ -	-C≡C-	2-pyridinyl	2-methoxyethyl
-(CH ₂) ₃ -	-C≡C-	3-pyridinyl	methyl
-(CH ₂) ₃ -	-C≡C-	3-pyridinyl	propyl
-(CH ₂) ₃ -	-C≡C-	3-pyridinyl	butyl
-(CH ₂) ₃ -	-C≡C-	3-pyridinyl	ethoxymethyl
-(CH ₂) ₃ -	-C≡C-	3-pyridinyl	2-methoxyethyl



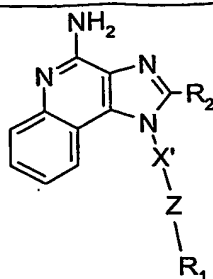
IIa

X'	Z	R ₁	R ₂
-(CH ₂) ₃ -	-CH=CH-	phenyl	methyl
-(CH ₂) ₃ -	-CH=CH-	phenyl	ethyl
-(CH ₂) ₃ -	-CH=CH-	phenyl	propyl
-(CH ₂) ₃ -	-CH=CH-	phenyl	butyl
-(CH ₂) ₃ -	-CH=CH-	phenyl	ethoxymethyl
-(CH ₂) ₃ -	-CH=CH-	phenyl	2-methoxyethyl
-(CH ₂) ₃ -	-CH=CH-	4-chlorophenyl	methyl
-(CH ₂) ₃ -	-CH=CH-	4-chlorophenyl	ethyl
-(CH ₂) ₃ -	-CH=CH-	4-chlorophenyl	propyl
-(CH ₂) ₃ -	-CH=CH-	4-chlorophenyl	butyl
-(CH ₂) ₃ -	-CH=CH-	4-chlorophenyl	ethoxymethyl
-(CH ₂) ₃ -	-CH=CH-	4-chlorophenyl	2-methoxyethyl
-(CH ₂) ₃ -	-CH=CH-	3-chlorophenyl	methyl
-(CH ₂) ₃ -	-CH=CH-	3-chlorophenyl	ethyl
-(CH ₂) ₃ -	-CH=CH-	3-chlorophenyl	propyl
-(CH ₂) ₃ -	-CH=CH-	3-chlorophenyl	butyl
-(CH ₂) ₃ -	-CH=CH-	3-chlorophenyl	ethoxymethyl
-(CH ₂) ₃ -	-CH=CH-	3-chlorophenyl	2-methoxyethyl
-(CH ₂) ₃ -	-CH=CH-	4-fluorophenyl	methyl
-(CH ₂) ₃ -	-CH=CH-	4-fluorophenyl	ethyl
-(CH ₂) ₃ -	-CH=CH-	4-fluorophenyl	propyl
-(CH ₂) ₃ -	-CH=CH-	4-fluorophenyl	butyl
-(CH ₂) ₃ -	-CH=CH-	4-fluorophenyl	ethoxymethyl



IIa

X'	Z	R ₁	R ₂
-(CH ₂) ₃ -	-CH=CH-	4-fluorophenyl	2-methoxyethyl
-(CH ₂) ₃ -	-CH=CH-	3-fluorophenyl	methyl
-(CH ₂) ₃ -	-CH=CH-	3-fluorophenyl	ethyl
-(CH ₂) ₃ -	-CH=CH-	3-fluorophenyl	propyl
-(CH ₂) ₃ -	-CH=CH-	3-fluorophenyl	butyl
-(CH ₂) ₃ -	-CH=CH-	3-fluorophenyl	ethoxymethyl
-(CH ₂) ₃ -	-CH=CH-	3-fluorophenyl	2-methoxyethyl
-(CH ₂) ₃ -	-CH=CH-	4-methoxyphenyl	methyl
-(CH ₂) ₃ -	-CH=CH-	4-methoxyphenyl	propyl
-(CH ₂) ₃ -	-CH=CH-	4-methoxyphenyl	butyl
-(CH ₂) ₃ -	-CH=CH-	4-methoxyphenyl	ethoxymethyl
-(CH ₂) ₃ -	-CH=CH-	4-methoxyphenyl	2-methoxyethyl
-(CH ₂) ₃ -	-CH=CH-	3-methoxyphenyl	methyl
-(CH ₂) ₃ -	-CH=CH-	3-methoxyphenyl	ethyl
-(CH ₂) ₃ -	-CH=CH-	3-methoxyphenyl	propyl
-(CH ₂) ₃ -	-CH=CH-	3-methoxyphenyl	butyl
-(CH ₂) ₃ -	-CH=CH-	3-methoxyphenyl	ethoxymethyl
-(CH ₂) ₃ -	-CH=CH-	3-methoxyphenyl	2-methoxyethyl
-(CH ₂) ₃ -	-CH=CH-	4-trifluoromethylphenyl	methyl
-(CH ₂) ₃ -	-CH=CH-	4-trifluoromethylphenyl	ethyl
-(CH ₂) ₃ -	-CH=CH-	4-trifluoromethylphenyl	propyl
-(CH ₂) ₃ -	-CH=CH-	4-trifluoromethylphenyl	butyl
-(CH ₂) ₃ -	-CH=CH-	4-trifluoromethylphenyl	ethoxymethyl



IIa

X'	Z	R ₁	R ₂
-(CH ₂) ₃ -	-CH=CH-	4-trifluoromethylphenyl	2-methoxyethyl
-(CH ₂) ₃ -	-CH=CH-	3-trifluoromethylphenyl	methyl
-(CH ₂) ₃ -	-CH=CH-	3-trifluoromethylphenyl	ethyl
-(CH ₂) ₃ -	-CH=CH-	3-trifluoromethylphenyl	propyl
-(CH ₂) ₃ -	-CH=CH-	3-trifluoromethylphenyl	butyl
-(CH ₂) ₃ -	-CH=CH-	3-trifluoromethylphenyl	ethoxymethyl
-(CH ₂) ₃ -	-CH=CH-	3-trifluoromethylphenyl	2-methoxyethyl
-(CH ₂) ₃ -	-CH=CH-	2-pyridinyl	methyl
-(CH ₂) ₃ -	-CH=CH-	2-pyridinyl	ethyl
-(CH ₂) ₃ -	-CH=CH-	2-pyridinyl	propyl
-(CH ₂) ₃ -	-CH=CH-	2-pyridinyl	butyl
-(CH ₂) ₃ -	-CH=CH-	2-pyridinyl	ethoxymethyl
-(CH ₂) ₃ -	-CH=CH-	2-pyridinyl	2-methoxyethyl
-(CH ₂) ₃ -	-CH=CH-	3-pyridinyl	methyl
-(CH ₂) ₃ -	-CH=CH-	3-pyridinyl	propyl
-(CH ₂) ₃ -	-CH=CH-	3-pyridinyl	butyl
-(CH ₂) ₃ -	-CH=CH-	3-pyridinyl	ethoxymethyl
-(CH ₂) ₃ -	-CH=CH-	3-pyridinyl	2-methoxyethyl

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this

invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.